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A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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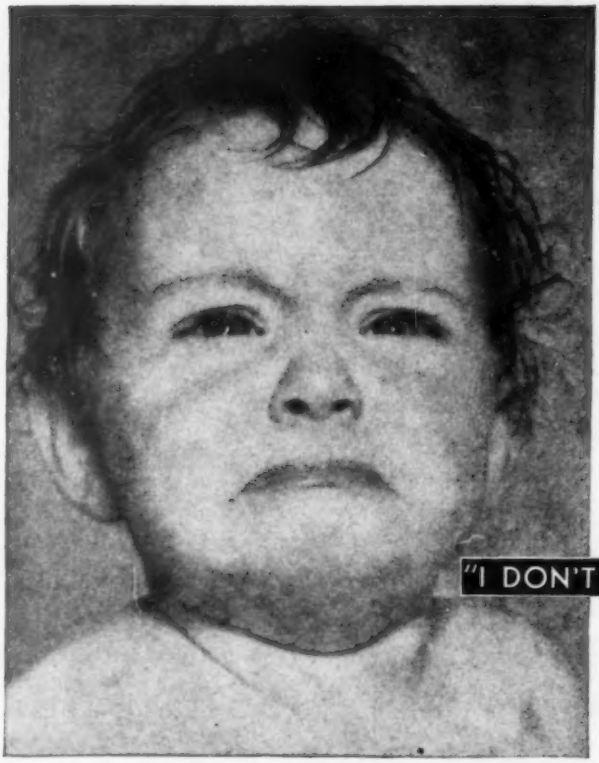

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The Journal of Pediatrics

VOL. III DECEMBER, 1933 No. 6

Original Communications

THE TREATMENT OF CHOREA BY INDUCED FEVER

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AND
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NEW YORK, N. Y.

SINCE October, 1930, most of the cases of chorea admitted to the Children's Medical Service of Bellevue Hospital have been treated with fever produced by the intravenous injection of typhoid-paratyphoid vaccine. We report in this paper on the results obtained in 150 cases and offer a comparison in 150 cases cared for on the same service prior to 1930. A preliminary report on the first 24 cases so treated was published in 1931.[1]

The volume of literature written about chorea is tremendous and is evidence of the lack of knowledge other than clinical about the disease. Neither the pathology nor the bacteriology is definitely established. The general opinion is that chorea is an encephalitis involving the basal ganglia and that it is due to the same toxic agent as that which causes rheumatic fever. The number of different treatments used for chorea makes a long list. With certain exceptions none have appreciably shortened the course of the disease.

In 1923 Tibor von Kern[2] reported three children with chorea to whom he gave intramuscular injections of milk at three- to five-day intervals. He felt that the course of the attacks had been shortened to three or four weeks' duration, but did not attribute the results to the fever produced. Several other reports occur in the German literature on this method of treatment. In 1927, I. Somogyi[3] published in an Hungarian periodical the results obtained in 30 cases. He felt that the course of the attacks was shortened to from three to five weeks. He gave the injections in the clinic and allowed the patients to go home to have the reaction. The authors who reported on the use of milk injections discussed the mecha-

From the Department of Pediatrics, New York University, and the Children's Medical Service of Bellevue Hospital.

This work has been done with the help of a grant from the Josiah Macy, Jr., Foundation.

nism of the foreign protein reaction and apparently did not consider the possibility that fever might be the effective factor.

In 1929, Roeder[4] first reported on the use of nirvanol (phenyl-ethyl-hydantoin) in chorea, and since then many articles have been published, most of them reporting on rather small series of cases. Apparently the course of an attack of chorea is definitely shortened by the use of the drug, at least in those cases which show fever as a result of the drug poisoning. In a very reasonable article on this subject Pilcher and Gerstenberger[5] state that the majority of patients who react to the drug with fever and morbilliform rash usually improve rapidly, while milder cases and those who do not react with fever and rash are not appreciably benefited. A few recent reports have commented unfavorably on this treatment, in that the authors failed to see beneficial results from the use of the drug. Here again the actual number of cases is small.

The danger of nirvanol lies in the poisoning which may result in serious complications and even death. Some such cases have been reported in the literature, and we have been told of others not reported. The complications may be nephritis, pneumonia, hyperpyrexia, or extensive and intractable skin lesions. On the other hand, Dennett and Wetchler[6] have reported a series of 72 cases of chorea treated with nirvanol with no serious complications whatever. They feel that the drug can be given safely to children in the hospital and under competent medical supervision.

In 1930 Mas de Ayala[7, 8] reported the case of a child with chorea to whom he gave relapsing fever. The result was very striking, and after the fourth bout of fever the improvement was complete. This author claims to have been the first to use fever therapy in chorea. This article appeared in the Spanish literature and was not found by us until some time after it had been published. Also, we, as well as others, have observed the beneficial effect of an intercurrent acute febrile illness such as measles, typhoid, acute tonsillitis, on chorea.

Dr. Nathaniel Chapman in 1818* said: "The intermittents do sometimes cure other diseases, as gout, rheumatism, acute and chronic; chronic cutaneous eruptions are frequently cured by them; spasmodic complaints as chorea, epilepsy, asthma, hysteria, mania and especially melancholia. I have told you it is the fashion in Europe to send patients with pulmonic complaints to miasmatic countries, and you have heard of the practice being used in our own country."

*Dr. Richard Kern of Philadelphia in a personal communication gives the source of this quotation as follows:

"There are in existence two large notebooks written apparently by an auditor of Dr. Chapman's lectures as delivered in the University of Pennsylvania School of Medicine in the year 1818. These notebooks are in longhand and are practically identical, suggesting that the writer was an individual who took down Dr. Chapman's lectures, possibly stenographically, and sold the copies to medical students.

"The copy which I was able to see several years ago is one that was in the hands of a medical student who was at the University at that time and has come down to one of his descendants, Dr. David L. Farley of our Medical Staff.

"The other copy is in the possession of the Dean of the Medical School, Dr. William Pepper."

Since the one factor common to treatment by milk injections, nirvanol intoxication, relapsing fever, intercurrent infections, and typhoid-paratyphoid vaccine injections is the production of fever, it is difficult to escape the conclusion that it is the fever which is beneficial in chorea, rather than the instrument which produces fever.

We first started to investigate the use of fever therapy in chorea in 1929. In March of that year a boy with severe chorea was given luminal as a sedative. He became intoxicated with the drug and developed a high fever. To our surprise the chorea began to clear rapidly after a few days of fever. The symptoms which this boy exhibited were similar to those which occur in nirvanol poisoning, namely rash and fever. Since luminal had been used by us before in chorea with no beneficial effect on the disease, it seemed logical to investigate the matter of fever therapy. For about a year we tried to produce fever with typhoid vaccine intravenously but found it impossible to get continuously satisfactory fever with this vaccine. However, an occasional good febrile result occurred followed by apparent improvement in the chorea, so that we were encouraged to continue the investigation. Finally, in the fall of 1930 we began to use typhoid-paratyphoid vaccine, and found that we could produce fever almost at will. The reason that typhoid vaccine and later typhoid-paratyphoid vaccine were chosen as the means of producing fever was that it is cheap, easily available, requires no elaborate set-up and is safe. Malaria was considered, but only luetic blood was available at that time. There is also a definite mortality among paretics from the malaria itself.

A method of procedure has been developed which produces satisfactory results. It should always be kept in mind that the object of the treatment is to shorten the attack by producing fever of at least 104° F. and that the vaccine is merely the means of obtaining the fever. We have found that a temperature of less than 104° F. is of little use, and feel that a fever of between 104° F. and 106° F. is the most effective.

Treatment with intravenous triple typhoid vaccine†

Aims:

1. To shorten the duration of the chorea, and therefore treatment is begun as soon after admission as possible.

2. *To get a daily temperature rise of 104°, or over, and to maintain it for as many hours as possible. Treatment being given daily until all signs of chorea have cleared.* A day when the temperature does not reach 104° is a wasted day!

3. To make the children as comfortable as they can be made during treatment.

Method:

1. Use New York City triple typhoid vaccine (containing 1,000 million *B. typhosus*, 750 million each of Para A and B per c.c.) a tuberculin syringe, and 24 G ¾" needle.

2. The vaccine should be boiled for three minutes before the first time it is used, and always kept in the ice box between treatments.

†Instructions developed for use of the internes on the Children's Medical Service at Bellevue Hospital.

3. First dose 0.05 c.c. TTV, undiluted, intravenously.

4. Second dose is governed by the reaction of the child to the first dose: for instance if the temperature the first day goes to 106° or over, repeat 0.05 c.c. the second day: if it goes to 105°± then give 0.075 c.c., and if to only about 104° then give 0.1 c.c. TTV.

5. Subsequent doses are determined entirely by the reaction of the child. In general increase the dose of vaccine by a larger amount each day. The average case may take: first day, 0.05 c.c.; second day, 0.075 c.c.; third day, 0.15 c.c.; fourth day, 0.25 c.c.; fifth day, 0.4 c.c.; sixth day, 0.6 c.c.; seventh day, 0.85 c.c.

However, this routine cannot be counted on to obtain adequate temperature elevation. A much larger increase may be necessary or:

6. Second doses on the same day may have to be given. If the temperature does not reach 103°, or only one or two readings in the neighborhood of 103° are obtained, then a second dose on the same day should be given. This second dose is usually one-third to one-half the original dose of the day. For instance if the first dose of the day was 0.6 c.c. and at the end of two hours the temperature is 103.2° and fifteen minutes later is 102.8°, then 0.2 c.c. TTV should be given at this time. If the temperature has dropped below 102°, then 0.3 c.c. should be given.

Note: In giving the second dose it is necessary to get it in as soon as possible after the temperature becomes stationary or begins to fall, otherwise a temperature curve like this instead of like this may be obtained. When it becomes obvious that a second dose may be necessary, have temperatures taken more frequently than one q hour, so that it will be known almost as soon as it begins to fall.

7. Keep the child well covered during the whole of temperature reaction. If the child becomes uncovered, temperatures do not stay up so well.

8. Treatment should be given daily unless condition of patient indicates need of a rest (severe vomiting, poor fluid intake, etc.) or unless the ward situation makes it impossible. *Never give first dose on a visiting day.* (The child may be taken out by the parents with a temperature of 104° if you do.)

9. Treatment should be given until all signs of chorea have disappeared. This is generally easy to tell in the mild and moderate cases, but may be more difficult in the severe ones. If there is much weakness and pseudoparesis present, there may be incoordination due to this weakness and to the prolonged treatment, after all signs of true chorea have cleared. When in doubt try massage and occupational therapy. The mild and moderate cases take on an average of 5-7 treatments and the severe cases 10-15.

10. Urines should be examined by the interne daily during treatment, for albumin and red cells. In our series we have not seen anything more than a transient albuminuria, and occasional red cells. However, hematuria has been reported to us. Therefore if the urine shows more than an occasional red cell, stop treatment until the hematuria clears.

11. Occasionally, especially in severe cases, a second course of vaccine may be necessary after an interval of several days or longer. In this case we have found that the size of the first dose of the second series depends on the interval. The following is a rough guide for dosage.

Interval of 1-3 days—Proceed as though there had been no interval.

Interval of 4-7 days—Give the same dose as that given on the last day of the first series.

Interval of 8-9 days— It is probably best to give a somewhat smaller dose than that given at the end of the first series, although if the reaction to that dose was poor, then the same dose may be repeated.

Interval of 10-20 days—We have had no patients who have fallen into this group. To be safe the dose should probably be decreased to about one-half the previous dose at 14 days and to one-quarter at 16 days.

Interval of 20 days—Series should be started over again at 0.1 c.c.

Care of patient during reaction:

1. Protein shock, with chill, severe headache, vomiting etc., generally occurs 20-50 minutes after the vaccine is given. The children are more comfortable if already hot; therefore extra blankets and hot water bottles should be given as soon as the vaccine has been given.

2. Codeine in maximum doses (¼ to ¾ gr. according to size of patient) relieves the headache to some extent. This should be given about 20 minutes after the vaccine on the first and second days of treatment, and should be given by hypodermic in thigh (to avoid a sore arm on which a tourniquet will be put the next day). After the first two days' treatment, the codeine may not be necessary, and it may therefore be left as an S. O. S. order, which may be given by mouth if the child is not vomiting.

3. Vomiting usually occurs during the first two or three reactions. Therefore lunch is omitted on these days. After this, vaccine may be given immediately after the noon meal. If for any reason the vaccine is to be given at another time during the day, see that provision is made for adequate food intake at some time during the day.

4. We have found that large drinks of fluids are likely to bring the temperature precipitously down, and therefore fluids should be limited during treatment. Small sips of water or fruit juice, however, make the children much more comfortable.

Treatment of hyperpyrexia:

1. Aspirin gr. 5, ice-cap to head, and a drink of water are usually given if two readings above 106 at fifteen-minute intervals are obtained. This should be done routinely if there is no doctor on the ward. However, some of the children have surprisingly little discomfort at high temperatures, and unless the temperature is going dangerously high, these procedures may be omitted, if the interne is present to assume responsibility for it.

2. For very high temperatures, 107° or more, all coverings should be taken off immediately and the child given a tepid sponge. Aspirin gr. 10 should be given by mouth unless the patient is vomiting or is unconscious, in which case give a double dose 15-20 gr. by rectum. Take the temperature every ten or fifteen minutes. If it continues to go up the child may be placed in a tub of water at 100°, the water then being gradually cooled. Sedatives and stimulants should be given as indicated.

Note: These very high temperatures seldom occur, and when they do usually they respond readily to the above treatment. They are not so terrifying as they look!

Routine orders usually written on the chart:

Vaccine given at 12 P. M. Take the temperature stat. and q 1 hr. until it returns to 99.6° (q ½ hr. when above 104° on the way up).

Extra blankets and hot water bottles stat.

Codeine gr. ½ (h. in thigh) at 12:20, and repeat after hrs. 3 if necessary.

Limit fluids to small sips of water, lemon or orange juice.

Aspirin gr. 5 and ice-cap to head for temperature over 106°.

Daily urine to laboratory during treatment.

Do not be afraid of high temperatures—they are necessary to cure the chorea.

Do not be afraid of large doses of vaccine.

Care of the patient during convalescence:

1. Children are kept in bed at least one week after completion of fever therapy—longer if the chorea has been severe, or if there has been any evidence of active carditis.

2. High calorie diet to make up for the loss in weight which usually occurs during treatment.

3. Occupational therapy (basket weaving, coarse sewing, etc.).

4. Transfusion if indicated for anemia.

5. Children are sent to a convalescent home from the hospital if possible.

Treatment of subsequent attacks by TTV.

There is apparently no increased sensitivity to the vaccine. In general we have found that *more* vaccine is required to obtain the desired temperature reaction when a child is being treated a second time with vaccine, than was required during the first course of treatment.

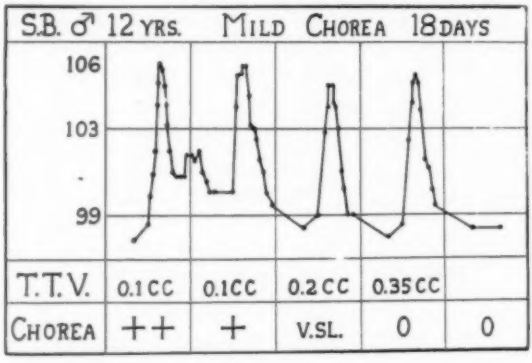

Fig. 1.—S. B. Mild chorea—first attack. Shows: (1) good temperature reactions with small doses of vaccine; (2) secondary rise on first day of treatment, which occurs in about 50 per cent of the cases; (3) good response to short course of treatment.

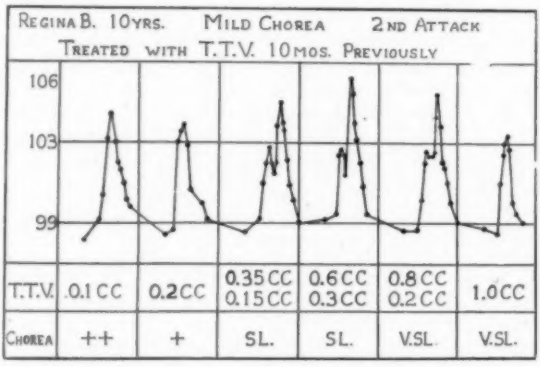

Fig. 2.—R. B. Mild chorea—second attack. First attack treated with T. T. V. ten months previously. Shows: (1) relatively larger doses of vaccine necessary; (2) second doses on same day; (3) longer course necessary in a second attack.

The average number of treatments in the 150 cases reported here was 6.24. In the mild cases the average was 5.14 treatments: in the moderate 6.47 and in the severe cases 8.88. The minimum number of treatments was 3, the maximum 18.

In some children, particularly the severe cases where there has been marked hypotonia, it may be difficult to decide just when the incoordinations are due simply to weakness rather than to chorea. In these cases massage and occupational therapy are given. If the weakness decreases with increased activity, we feel safe in saying the attack is over. If the

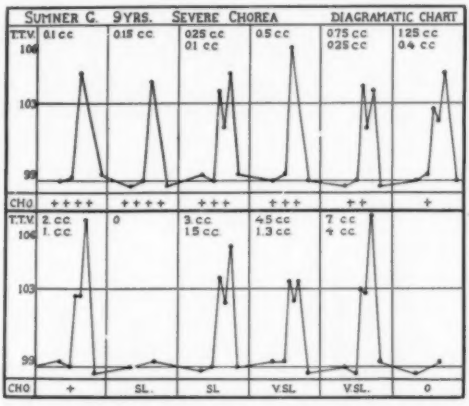

Fig. 3.—G. Severe chorea of two weeks' duration. (Case treated at The Nursery and Child's Hospital, courtesy of Dr. Louis Schroeder.) Shows: (1) severe chorea responding readily to vigorous treatment; (2) good temperature reactions; (3) large doses of vaccine necessary.

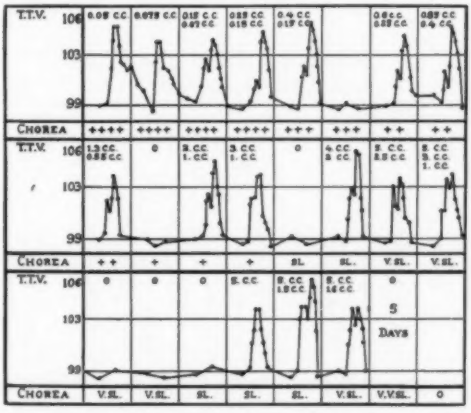

Fig. 4.—S. R. Severe chorea of one month's duration. Shows: (1) case difficult to cure, requiring long course of treatment; (2) relatively poor temperature reactions; (3) relapse of chorea on rest after thirteen treatments.

incoordination becomes worse, it denotes continued activity of the disease and treatment is resumed. In the ordinary moderately severe or mild case there is usually little difficulty in knowing when the attack has been arrested.

The types of febrile reaction obtained by this method are shown in Figs. 1-4.

While the majority of cases respond readily to fever therapy, a certain small proportion are disappointing in their results. Fig. 4 shows a case of this sort, in which, although the chorea improved from severe to very mild in a reasonable length of time, i.e. ten days, definite choreiform movements persisted for more than two weeks longer. In general

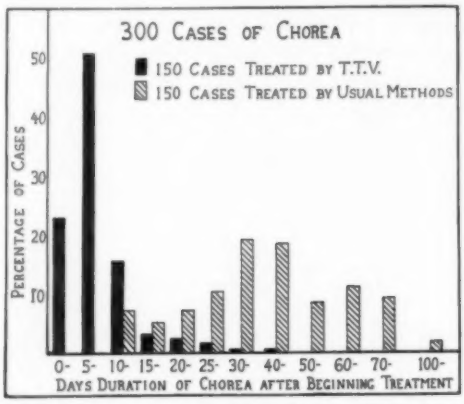

Fig. 5.—Duration of the chorea after beginning of treatment in 300 cases.

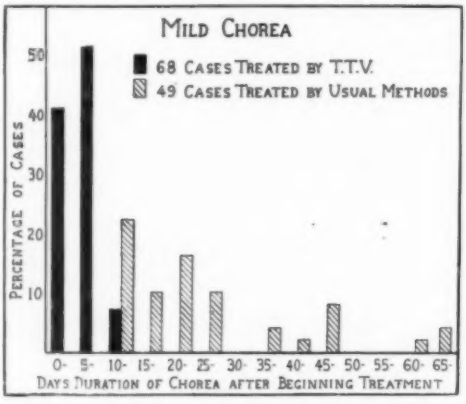

Fig. 6.—Duration of the chorea after beginning of treatment in 117 mild cases.

these difficult cases are likely to be repeaters, or cases in which the duration of the present attack has been long before treatment was begun. While most of these difficult cases fall in the severe group, an occasional one is found in the moderate and even in the mild group. In this latter group it is particularly difficult at times to determine how much if any of the residual movements is due to true chorea, and how much to habit. Of 150 treated cases, only 10 per cent responded to

treatment in this way. The longer the course of treatment the more difficult it becomes to obtain adequate febrile reactions, and this fact increases the difficulty in treating some of the more severe cases. In general, the results are prompter and more complete in cases treated early in their first attack.

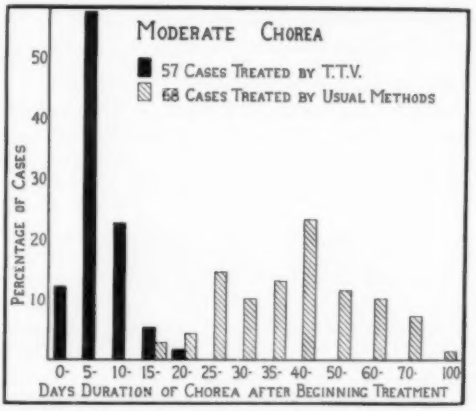

Fig. 7.—Duration of the chorea after beginning of treatment in 125 moderate cases.

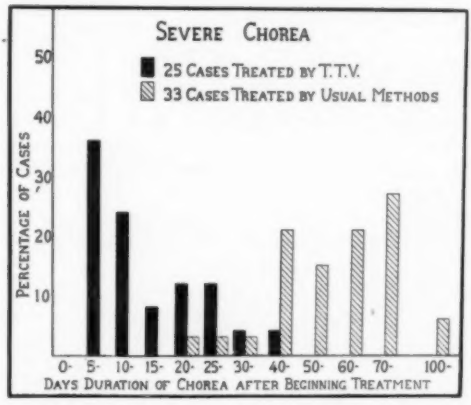

Fig. 8.—Duration of the chorea after beginning of treatment in 58 severe cases.

The advantages of the typhoid-paratyphoid vaccine method of producing fever are that it is cheap, safe, simple, and produces the desired therapeutic result. The fever follows immediately after the injection, in contrast to the one to two weeks' interval which must elapse before the toxic effects of nirvanol appear.

Because we thought that a temperature maintained at a high level for four or five hours might be more effective than the type of fever obtained

with vaccine alone, and thus necessitate fewer treatments, we tried using a combination of vaccine plus blanket packs in a number of cases. We found that we could maintain the fever for several hours, and got temperature curves similar to those obtained by the radiotherm and diathermy methods. However, the children were more exhausted the following day than when vaccine alone was used. A day without treatment was therefore often necessary, and time was lost. We finally discontinued this method because of the following case:

A. P., a girl twelve years old, was admitted in her third very severe attack of chorea. We had treated her second attack a year before with a very good result. Treatment was started as usual, and she showed marked improvement. The fourth dose of vaccine was given at 8:30 one morning. Her temperature reached a maximum of 101°, and then dropped until at 3:30 it was 100° by rectum. In other words she had almost no reaction to the vaccine, and it was all over by mid-afternoon. Because of the poor febrile response to the vaccine she was blanketed about 3:30 P. M. Her temperature rose slowly to 102.8° at 6 P. M., and she was in good condition. The nurse went back to her fifteen minutes later and found that her temperature was 109.8° and that she was unconscious. The resident and internes immediately took measures to reduce the fever and it came down to 101° within three hours. At 11:30 P.M. she began to have convulsions which lasted several hours; the temperature rose to 103° the next morning and she died in the afternoon. Autopsy showed massive lobular pneumonia of both lungs, early vegetative endocarditis of the mitral valve, which had not been sufficient to produce physical signs, and microscopic evidence of past inflammation of the aortic valve. Whether the pneumonia had been caused by the means taken to reduce the temperature we cannot say; it was not suspected before the child was put in the pack.

Study of the brain by Dr. Lewis Stevenson showed:

"A longitudinal section through basal ganglia shows very many distended blood vessels. In the lenticular nucleus and caudate nucleus there are also very many distended blood vessels and to some extent in the posterolateral part of the optic thalamus. Apparently, this is true of the optic radiations as well. There is apparently a slight amount of hemorrhage in the posterior horn of the lateral ventricle, staining the ependyma. In the left hemisphere these distended vessels appear in the internal and external capsules and again in the optic radiation and to some extent in the optic thalamus near the internal capsule.

"Microscopic Examination of Brain.—Microscopic sections of caudate nucleus, lenticular nucleus show a mild degree of encephalitis evidenced by small round celled infiltration about some of the smaller vessels. Section of different parts of cortex failed to show this reaction; there is no evidence of meningitis."

This case demonstrated entirely too well what we already knew, namely, that the temperature can rise very high and very rapidly from the use of packs, which cause fever by preventing loss of body heat by radiation. It is important to realize that this fatality was not caused by the vaccine. This is the only death in our series of treated cases.

On the other hand two other children whose temperatures went over 109° from the packs sustained no ill effect, and the beneficial effect on the chorea was definite. The highest temperature from vaccine alone was 108° and this occurred in only one case.

RESULTS

The results with fever therapy in chorea seem to us rather striking. We have made no attempt to run a control series, since this would involve subdivision of cases into groups according to age, sex, number of attacks, duration and severity of attack, and season of the year. This would necessitate a very large number of cases. Moreover, it has been known ever since Sydenham first described chorea that the duration is prolonged, that the average attack lasts six to ten weeks, and that even a mild case may last for months.

For comparison with our results, however, we have gone back over the records of children with chorea treated in Bellevue between 1920 and 1930. We found 150 records with sufficiently detailed and frequent progress notes to determine the actual duration of the chorea in the

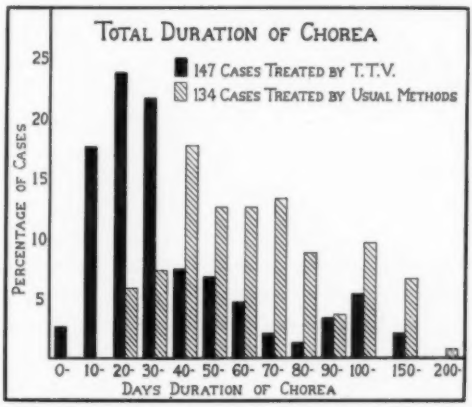

Fig. 9.—Total duration of the chorea in 281 cases. This includes, in the treated group, duration before admission plus observation period plus duration of movements after beginning of treatment; in the untreated group, duration before admission plus duration in the hospital.

hospital. The treatment given these children included Fowler's solution, sodium salicylate, calcium lactate, thyroid extract, high caloric diet, starvation, hot and cold packs, hydrotherapy, autoserum therapy, rest, catharsis, bromides, luminal, and other sedatives.

The cases in both the comparative and the treated series have been grouped as mild, moderate and severe. In the comparative group there are a number of children who were admitted as mild cases which became moderate, and others admitted as moderate which became severe. These were put into the moderate and severe groups respectively.

The mild group consists of cases of undeniable chorea, but with little functional incapacity. The moderate group includes the cases with continuous, incoordinate movements, with some speech impairment. Such children have difficulty in performing voluntary acts, and the gait

is that of a drunken person; they can run better than they can walk. The severe group is composed of those with marked hypotonia, and pseudoparesis. The hypotonia may be so great as to mask the choreiform movements. These children are unable to speak intelligibly, have difficulty in chewing and in swallowing even liquid food. They have no control whatever over their movements or emotions, and may be unable to try to perform voluntary acts.

The duration of the chorea in the hospital in the group used for comparison, and the duration in days after beginning of fever treatment is shown in Table I.

TABLE I

TYPE	NUMBER OF CASES	AVERAGE DURATION IN DAYS	RANGE IN DAYS
MILD			
Comparative group	48	27.4	10-67
Treated group	68	5.72	2-14
MODERATE			
Comparative group	68	44.	15-120
Treated group	57	8.56	3-22
SEVERE			
Comparative group	33	62.4	24-180
Treated group	25	15.8	5-47
WHOLE SERIES			
Comparative group	150	42.6	10-180
Treated group	150	8.5	2-47

A comparison of the two groups confirms the impression that the cases of chorea at Bellevue treated by means other than fever had a considerably longer duration than those treated by induced fever. Figs. 5 to 9 show this graphically.

The question arises whether a somewhat heroic treatment is justified in a disease which in itself is rarely fatal. We feel that it is for the following reasons. It reduces the time spent in the hospital and hence cuts down the expense to the institution. It lessens the period of time lost from school by the child. Although considerable nursing care is required during the treatment period, the nurses are relieved of the prolonged care of an untreated case. The mental agony endured by a person with chorea seems to be great. Several older children who have been treated in well-advanced attacks have come back to us saying that they felt an attack coming, even before we ourselves could have been sure of the diagnosis, and would we "please give them the needles right away" so they could get back to school and not have a bad attack. A sixteen-year-old boy who had had two prolonged attacks was recently treated in his third attack on the adult service at Bellevue Hospital. When asked what he would do if he got a fourth attack, his reply was, "I'd come back for more needles." This is the reaction of those who have had treated and untreated attacks, and seems to us justification for the treatment.

Of the 150 patients with treated attacks reported here, 28 patients already had organic rheumatic heart disease. None of these children were harmed in any way by the treatment. Eight children who had definite evidence of active carditis at the time treatment was started, had lost the signs of activity by the time the treatment of the chorea was over. We feel, therefore, that the presence of either active or inactive heart disease is not necessarily a contraindication to treatment. We would hesitate to give the treatment in the presence of a very severe carditis as evidenced by a pericardial friction rub, but fortunately this combination seldom occurs.

It has been gratifying to hear from physicians in various parts of the country that this method of treating chorea has been used satisfactorily in about 100 other cases. We suspect that those who failed to get good results have probably not followed our technic, and have therefore not obtained good febrile reactions.

A chorea clinic has been established to follow these cases, and we intend to observe them for a period of at least five years from the time of treatment. There seems to be no rational basis for anticipating a reduction in the number of recurrences of chorea in these treated cases. However, this question of recurrences, as well as that of development of heart disease, is being carefully watched and at the end of the observation period data on both treated and untreated cases will be available. So far we have had about 98 per cent follow-up of cases. The number of recurrences is relatively small, but since the treatment has been in use only about two and one-half years, and since chorea may recur after a lapse of a number of years, our present figures on recurrences have no final value.

Investigators are working continually to perfect methods of producing fever, and will doubtless some day devise an apparatus which will be safe in ordinary hands and will lack the unpleasant features of foreign protein shock or of radiothermy and diathermy, and which will at the same time be neither expensive nor elaborate. Until then intravenous injections of typhoid-paratyphoid vaccine can be used as a fairly reliable and safe method of treating chorea.

SUMMARY

Intravenous injections of typhoid-paratyphoid vaccine as a means of inducing fever have been used in 150 attacks of chorea. Comparison of the duration of chorea in the hospital in 150 attacks treated by other methods show that the duration of the attacks has been reduced from an average of 27.4 days in the mild untreated cases to 5.72 in the mild treated cases; from 44 days in the untreated moderate cases to 8.56 in the moderate treated cases; and from 62.4 days in the severe

untreated cases to 15.8 days in the severe treated cases. We conclude, therefore, that fever therapy is a satisfactory method of treatment of chorea.

We wish to express our great appreciation to Dr. Charles Hendee Smith for his interest in this study and his very helpful encouragement.

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THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN WITH ANTIPNEUMOCOCCUS SERUM

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ANTIPNEUMOCOCCUS serum has been used extensively in the treatment of pneumonia in adults. For some types the results have definitely proved its value in reducing the mortality rate. The purpose of this paper is to report the results of antipneumococcus serum therapy in the pneumonias of infants and children for similar types of pneumococci and for the more recently isolated types so frequently found in infants and children.

Lobar pneumonia in children (two to twelve years) is notably a benign disease; under two years, it approaches in severity the pneumonia of adults. Bronchopneumonia is distinctly a very serious disease, both in its course and in its mortality rate. For the past three years on the Children's Medical Service at Bellevue Hospital, the mortality rate of bronchopneumonia is approximately 60 per cent and of lobar pneumonia in infants under two years approximately 20 per cent. These figures refer to pneumonias irrespective of etiologic agent. These percentages contrast sharply with a mortality rate of 5 per cent for lobar pneumonia in children over two for the same period of time on the same wards. On the other hand, the mortality rate of pneumonia in adults varies from approximately 20 per cent to 45 per cent, depending upon the type of infecting organism. Obviously other criteria than those used for adults must be employed in the evaluation of antipneumococcus serum therapy in infants and children. The criteria here used are the effect on the severity and progress of the disease as judged by the duration of the pneumonia and the effect on complications.

This study was begun in January, 1932, and included a clinical and bacteriologic observation of 368 patients with all types of pneumonia. This report comprises 207 patients; the remaining 161 are not included as they represent patients having pneumonia due to bacteria other than the pneumococci types for which we have specific serums. During this investigation therapeutic serum was available for the following types of pneumococci: I, II, IV, V, VI A and B, VII, XIV, XVIII, XIX, and XXII. New serums have been produced for other types since the beginning of this study.

From the Department of Pediatrics, New York University Medical School, and the Children's Medical Service, Bellevue Hospital, and the Research Laboratory of the Department of Health, New York City.

This investigation was made possible by a grant from the Commonwealth Fund to the New York University for research in pneumonia. It has been conducted at the suggestion of and under the direction of Dr. William H. Park. Thanks are also due to Dr. Charles Hendee Smith, director of the Children's Medical Service, Bellevue Hospital, for his criticisms and advice. The bacteriologic typing was done under the supervision of Miss Julia Vinograd. Assistance was also given during the first year by the Altman Foundation.

Choice of Material.—Only those patients are here recorded whose laryngeal swab cultures revealed pneumococci of a type for which therapeutic serum was available. A full report of the bacteriology of pneumonia in infants and children will be published later. Patients who died within twenty-four hours of admission to the hospital are excluded from this report. Approximately alternate cases were treated with the serum, except that no patient from two to twelve years of age was treated later than the fifth day of disease, usually not later than the fourth, and no infant under two years, later than the sixth day of disease. In tabulating the results, similar age groups were used; e.g., infants with lobar pneumonia untreated were not included in the control group unless *infants* with *lobar* pneumonia were treated with antipneumococcus serum for the same pneumococcus type. The duration of the disease is longer in infants, and the mortality rate is higher.

The diagnosis of lobar pneumonia was made on the basis of characteristic clinical course, physical examination, and roentgenographic evidence of pneumonic involvement. An x-ray photograph was taken at least once during the course of the active disease. The left eccentric view of every patient with left lower lobe pneumonia was also used. Some patients presented a clinical picture similar to that of pneumonia, but the diagnosis was not confirmed by x-ray or consistent physical signs; these cases were excluded from the report. This group, however, is small, comprising 7 untreated cases, 2 having Type XIX pneumococci, 3 Type VI, and 1 each of Types IV and XXII. All of these pneumococci are commonly found in the throats of normal infants, particularly Types VI and XIX.

A careful differentiation between lobar pneumonia and bronchopneumonia must be made. 1. As a rule, a crisis is not observed in bronchopneumonia as in lobar pneumonia, either in the treated or control group. Consequently, a determination of the duration of the disease becomes almost impossible. 2. The mortality rate is higher in bronchopneumonia. 3. Bacteriologic study reveals a much lower incidence of pneumococcus pneumonia in the bronchopneumonia group. For some years a study of pneumonia has been under way by Dr. Charles Hendee Smith and coworkers on the Children's Medical Service at Bellevue Hospital. A correlation of the clinical course, the roentgenographic findings, and the pathologic picture has been made. It has become apparent that lobar pneumonia and bronchopneumonia have a different clinical course, physical signs, x-ray picture, prognosis, and pathologic findings. Criteria for better differentiation between lobar pneumonia and bronchopneumonia have been described in abstract by Smith, Graef, and Andrews.[1]

METHOD

Bacteriologic Study.—Laryngeal swabs were taken on all patients with pneumonia by irritating the pharynx with a long cotton swab and pro-

voking a cough productive of mucus which is caught on the swab and put into plasma broth. A laryngoscope was not used. The method described, if carefully employed, gave sufficiently accurate results for practical purposes. Lung suction punctures have not been used for obtaining material for culture.

Laryngeal swab cultures have been checked on repeated days, and, in lobar pneumonia, have correlated to a great extent with bacteriologic study of postmortem lung punctures made immediately after death. Raia, Plummer, and Shultz[2] evaluated the throat swab culture method by correlating the cultures obtained with the bacteriologic study of other body fluids, and found an 88 per cent accuracy. A small percentage of error was also found in this study. On several occasions pneumococci obtained from the laryngeal swab were probably normal inhabitants of the throat and not pathogenic for the patient. In some of these cases, blood cultures were positive for streptococci rather than pneumococci. In other cases, a pneumococcus (usually Type VI, a frequent inhabitant of the throat in children) might be isolated from only one swab, but never cultured again from repeated swabs on the same patient.

Material obtained from the laryngeal swab was injected into a mouse, and the original swab was used in streaking blood agar plates. The Sabin[3] method for rapid typing of the mouse's peritoneal exudate was employed. For the past month, the direct typing by the Neufeld reaction, as recently described by Sabin,[4] has been used in selected cases with promising results. Direct typing will be of great value in serum therapy, especially in children, with a saving of from ten to twelve hours in determining the pneumococcus type.

Serum Administration.—The serums used in this investigation were obtained from the Department of Laboratories and the Bureau of Research, New York City, and were prepared and refined by Miss Georgia Cooper. Patients receiving serum were given a skin test, using one-tenth of a centimeter of a 1:10 dilution of the concentrated serum intracutaneously, and an ophthalmic test with this same diluted serum. Only one patient had a positive intracutaneous and ophthalmic test. This patient was not treated. A patient with a positive ophthalmic test should not be treated. The dosage for twenty-four hours was approximately 300 to 800 units per pound of body weight, varying in relation to the severity of the disease. The serums varied in titer from 400 to 2,500 units per c.c. Usually 2 c.c. (irrespective of units) of serum were given intravenously as the first dose for an infant under two years, and 5 c.c. for a child. Slow administration of intravenous serum is very important. Practically, the subsequent dosage was regulated by repeating the first dose if the drop in temperature was appreciable six hours after the first injection of serum, or doubling the first dose if the effect on the temperature curve was only slight. The average dosage for twenty-

four hours was from 6 to 9 c.c. for an infant and from 15 to 25 c.c. for a child. One dose was usually given after the temperature had remained below 100° F. for a period of from two to four hours. Frequently, three or four doses were sufficient and never were more than seven given. Intravenous administration of serum is so much more effective than the intramuscular method that the first one or two doses should be given intravenously; after this first dosage, serum may be given intramuscularly with good results.

Serum Reactions.—The amount of serum administered is usually too small to give serum sickness. Only one patient of the 82 treated developed this reaction. One six-month-old baby, having a negative ophthalmic and skin test, died immediately (three to five minutes) after the intravenous injection of 2 c.c. of antipneumococcus serum. There were no urticarial wheals; however, the death appeared to be associated with serum therapy. Unfortunately, an autopsy was not granted. The delayed reaction following serum therapy was seen rather frequently in varying degrees of severity. From thirty to sixty minutes after intravenous injection of serum a chill, occasionally slight cyanosis, dyspnea, and a thermal reaction, usually amounting to a rise of 2° F., have been observed. This type of reaction is constantly becoming less frequent with the increased refinement of serum. No such reactions occurred following intramuscular injection of serum.

RESULTS

The distribution of the cases studied according to age group is given in Table I. Only 2 of the 36 patients with bronchopneumonia reported were over two years of age.

The group of infants treated with serum is smaller than the children's group because infants commonly have pneumonia due to pneumococci for which we have no therapeutic serum. Table II illustrates that 47 per cent of the 116 infants had lobar pneumonia due to an organism for which we have no specific serum, as compared to 32 per cent of the 278 children with lobar pneumonia.

The predominant infecting organism in the lobar pneumonia of children is pneumococcus Type I, occurring in 32.5 per cent of all children's lobar pneumonia and in 47 per cent of the total 109 children in the *treatable group.* For infants, the predominant pneumococcus in the treatable cases of lobar pneumonia is Type XIV, representing 27 per cent of all infants' pneumonia and 33.6 per cent of the 116 treatable group. In infants with bronchopneumonia, pneumococcus Type XIX occurred rather commonly and had a high mortality rate. This organism was frequently associated with streptococcus or hemolytic staphylococcus (5 of the total 11 patients; all of the 5 died). The significance of pneumococcus Type XIX as the etiologic agent of the disease in such instances was difficult to determine. Three postmortem lung puncture cultures in these 5 patients had no pneumococci. The pre-

TABLE I

DISTRIBUTION OF TYPES OF PNEUMOCOCCI IN SERUM AND CONTROL GROUP OF CASES

TYPE	AGE YEARS	TREATED				UNTREATED				TOTAL
		LOBAR PNEUMONIA		BRONCHO-PNEUMONIA		LOBAR PNEUMONIA		BRONCHO-PNEUMONIA		
		TOTAL	DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	
I	2-12	22	–			30	1			52
	under 2	–	–			3*	2*			3
II	2-12	4	–			4	–			8
	under 2	–	–			–	–			0
IV	2-12	1	–			2	–			3
	under 2	–	–			–	–			0
V	2-12	3	–			3	–			6
	under 2	–	–			2	–			2
VI	2-12	5	–	–	–	10	–	1	1	16
	under 2	5	1†	1	1	6‡	3‡	3	3	15
VII	2-12	1	–	–	–	3	–			4
	under 2	4	1§	–	–	3	–			7
XIV	2-12	8	–	1	–	12	–	–	–	21
	under 2	17	2	3	2	22	2	5	3	47
XV	2-12			–	–			–	–	0
	under 2			1	–			–	–	1
XVIII	2-12			–	–			–	–	0
	under 2			2	2			1	1	3
XIX	2-12			–	–			–	–	0
	under 2			2	1			9	8	11
XXII	2-12			–	–			–	–	0
	under 2			2	–			–	–	2
Mixed types VI, III, XIX	under 2					1	–			1
VI, XVII	under 2							1	–	1
VI, XVIII	under 2							1	–	1
VI, VII	under 2							1	1	1
XIV, III	under 2							1	–	1
XIX, XI	under 2							1	–	1

*Excluded from study because no *infants* were treated with Type I serum.

†Excluded from mortality table because case of meningitis complicating pneumonia when treated.

‡Excluded from mortality table as meningitis complicating pneumonia when treated—two such cases.

§Excluded from mortality group; died of *Staphylococcus aureus* lung abscesses and empyema—autopsy.

TABLE II

INCIDENCE OF LOBAR PNEUMONIA IN INFANTS AND CHILDREN

(Bellevue Hospital, January, 1932—July, 1933)

AGE (YEARS)	NO. OF CASES			
	UNTREATED		TREATED	TOTAL
	NO SERUM AVAILABLE	SERUM AVAILABLE (CONTROL GROUP)		
under 2	54	36*	26†	116
2-12	51	65	44	160
Total	105	101	70	276

*Including one case of meningitis.

†Including two cases of meningitis and three Type I pneumococcus in infants.

dominance of Type XIX might also be due to seasonal variation; there were more pneumococcus Type XIX infections both in patients with upper respiratory infection and with pneumonia in 1932-1933 than in the winter of 1932. Pneumococcus Type VI occurred frequently in infants in both lobar pneumonia and bronchopneumonia.

The mortality rate for both bronchopneumonia and lobar pneumonia is shown in Table III.

TABLE III

MORTALITY RATE IN TREATED AND CONTROL GROUP

	BRONCHO-PNEUMONIA		LOBAR PNEUMONIA		LOBAR PNEUMONIA AND BRONCHO-PNEUMONIA		MORTALITY PER CENT
	TOTAL	DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	
Cases treated	12	6	69*	2	81	8	9.8
Cases untreated	24	17	96†	3	120	20	16.6

*Excluding one case of pneumococcus meningitis complicating pneumonia when treated.

†Excluding two cases of pneumococcus meningitis associated with pneumonia, and three infants with Type I lobar pneumonia.

Although the percentage of mortality for the treated cases is lower than that for the control group, the entire series is too small to warrant a definite conclusion as to the efficacy of serum in reducing the mortality rate.

The bronchopneumonia group is small, not because of the infrequency of the disease, but because we are more often unable to obtain pneumococci from *repeated* laryngeal swabs. Of the 90 patients with bronchopneumonia studied, only 50 had pneumococci in the cultures from laryngeal swabs. Of these 50, 26 died and cultures of postmortem lung punctures made *immediately* after death on 7 showed hemolytic staphylococci or streptococci, but no pneumococci could be isolated; from 9 patients pneumococci were cultured from postmortem lung punctures. No postmortem lung puncture was done on 9 of the 26 patients, and 1 puncture was sterile.

An objective criterion for the efficacy of antipneumococcus serum in *lobar* pneumonia is shortening the duration of the disease. A crisis usually occurred from twelve to twenty-four hours following the introduction of serum therapy, frequently after the administration of only 7 to 10 c.c. in twelve hours' time. In infants, this period is prolonged from twenty-four to forty-eight hours. The crisis was judged by fall in pulse rate and respiratory rate, and other evidences of loss of toxicity.

Charts 1, 2, and 3 show the effect of serum on the duration of the disease. The day of crisis of all patients with lobar pneumonia due to pneumococci for which we have therapeutic serum is given in Chart 1. A crisis was observed by the fifth day of the disease in 60 per cent of the

49 patients treated with serum as compared to 20 per cent of the 79 patients in the control group. Many of the serum treated patients had a crisis before the fifth day of the disease.

The most consistently satisfactory results have been obtained with pneumococcus Types I and XIV serums. Chart 2 illustrates the day

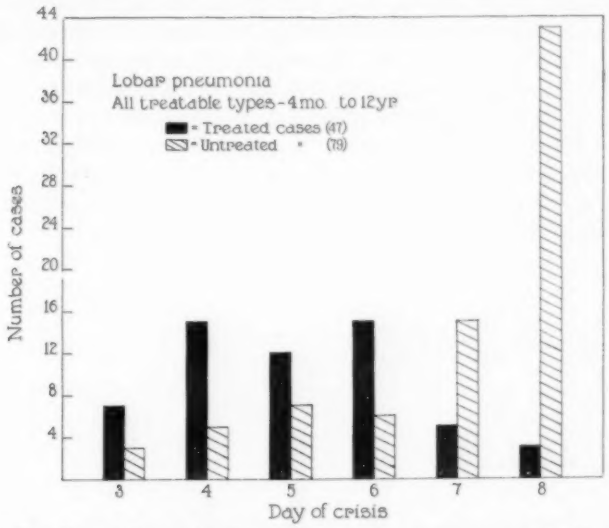

Chart 1.—Duration of disease in all patients receiving serum compared with a control untreated group. Greater number of treated cases show early crisis.

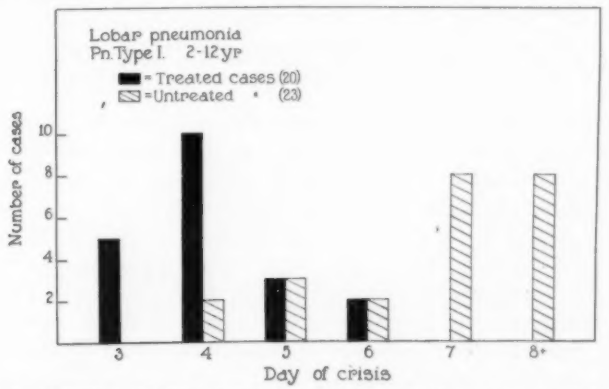

Chart 2.—Duration of Type I pneumococcus pneumonia among treated children compared with untreated control group. The course of the disease is definitely shorter in the treated group. Seventy-five per cent of the treated patients had a crisis before the fifth day, as compared with 10 per cent for the control group.

of crisis of patients with pneumococcus Type I pneumonia in children. It can be seen at a glance that serum definitely shortens the disease; a crisis as early as the third day in 5 of the 20 treated cases is noted,

whereas not a single patient of the 25 untreated cases had such an early crisis. The duration of the disease was never longer than six days in any patient receiving serum (Type I); while in 16 of the 23 control group a crisis occurred after the sixth day. In short, 75 per cent of the treated patients had a crisis before the fifth day as compared to 10 per cent for the control group. Antipneumococcus Type XIV serum has been similarly effective in shortening the disease in both infants and children as shown in Chart 3. The duration of lobar pneumonia in infants on the average is several days longer than in children. None of the 18 patients receiving serum had a crisis later than the seventh day, while the duration of the disease in 18 of the 27 untreated patients was longer than seven days. In other words, a crisis was observed in 80 per cent of the 18 patients before the seventh day as contrasted with 19 per cent (5 of the 27) of the control group.

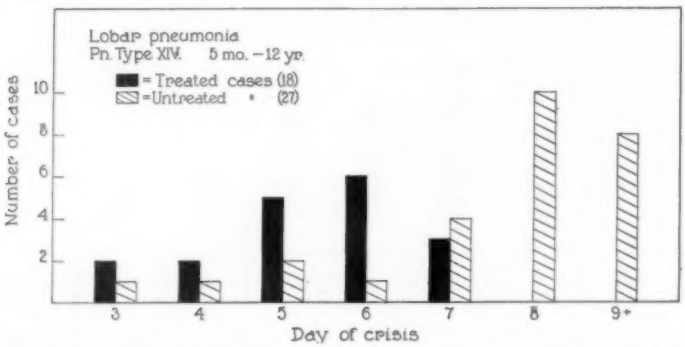

Chart 3.—Duration of Type XIV pneumococcus pneumonia of control and treated group for all ages. The treated patients had later crises, eighth and ninth days; no similar case in the treated group. The disease is shorter in the treated patients.

Although Chart 1 definitely suggests that serum is efficacious in shortening the disease, all serums are not equally effective. Chart 1 represents largely (80 per cent treated, and 63 per cent untreated) the results with antipneumococcus serums Types I and XIV. On the other hand, the results of antipneumococcus Type VI serum do not seem to have been so decisive. An analysis of 21 patients, 7 treated and 14 untreated, reveals no appreciable difference in the two groups. In fact, 2 untreated patients had a crisis as early as the third day, whereas the earliest for the treated group was the fourth day. A probable explanation for these observations aside from the possible inefficacy of antipneumococcus Type VI serum is the difficulty of diagnosis. Since pneumococcus Type VI A and B is a frequent inhabitant of the throats of infants and children, errors in diagnosis with this organism may be easily made.

The medical histories were taken with great care to determine the exact day of onset of the pneumonia; nevertheless, there was a small

number in each group in which the duration of the disease was indeterminate due to inability to date the onset or to date the crisis; as for example, in the development of an empyema.

On the whole, the serum treated group showed signs of greater toxicity before treatment than the nontreated group. This observation is in part indicated by the fact that there was a greater number of two lobe pneumonias in the serum group; 13 of the 69 (18 per cent) treated patients had two or more lobes involved, whereas only 8 of the 94 (8 per cent) control group had pneumonic consolidation of more than one lobe.

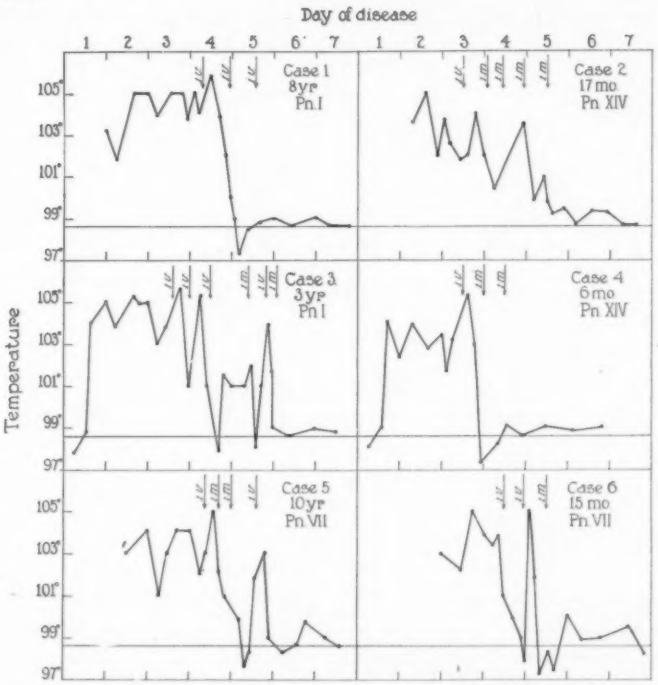

Chart 4.—Temperature curves of selected patients, showing usual response to antipneumococcus serum in *lobar* pneumonia. The arrow represents serum administration of Types I, XIV, and VII antipneumococcus serum, intravenously (i.v.) or intramuscularly (i.m.). Cases 1 and 4 indicate a common type of response. The latter developed lobar pneumonia in the hospital. Case 3 also developed lobar pneumonia in the hospital and illustrates the result of inadequate treatment; a second dose of serum should have been given on the fourth day of the disease. Small quantities of serum were used in Cases 1, 4, 5, and 6.

The response to the administration of serum can best be seen by reference to the temperature charts of a few selected cases showing typical response (Chart 4). Pneumococcus Type I is the predominant type for children and Type XIV for infants in this series. The thermal reaction following intravenous injection is also shown, particularly in Case 3 where a certain lot of serum having a high content of chill-producing

fraction was used. The loss of toxicity following serum administration is as impressive as the drop in temperature and is correlated with it, sometimes antedating the final temperature fall to normal. Case 2 illustrates the use of intramuscular serum injections after an initial intravenous dose.

Patients with bronchopneumonia show a different response to serum treatment. A crisis is not usually observed as in the lobar pneumonia group, and hence a fall in temperature cannot usually be used as a criterion for the efficacy of serum. We treat bronchopneumonia patients for only forty-eight hours, using the dosage of from 500-1000 units per pound of body weight for a twenty-four-hour period (or 10-15 cc. in 3-4 doses per day). Chart 5 represents the temperature curves

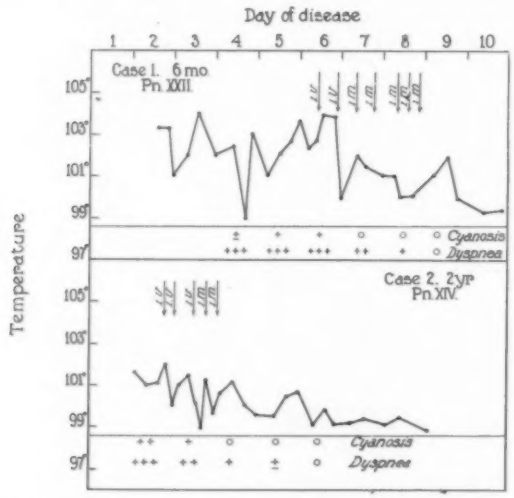

Chart 5.—The temperature curve of two patients with *bronchopneumonia* receiving antipneumococcus serum Types XXII and XIV. Temperature response is not like that in lobar pneumonia. (See Chart 4). Improvement is clinical as indicated below in decreasing cyanosis and dyspnea. More frequent and larger dosages of serum are necessary in bronchopneumonia.

of patients with bronchopneumonia who received serum. Both patients were very sick, with cyanosis and marked dyspnea. These symptoms were practically lost after forty-eight hours of treatment and were diminished after only twenty-four hours. There is no crisis, however, and a comparison of these temperature curves with those in Chart 4 reveals this fact.

A study of the duration of the disease with reference to the period of hospitalization is shown in Chart 6. It becomes apparent that admission to the hospital early in the disease does not in itself act to shorten appreciably the duration of Type I pneumococcus pneumonia in the same age group. To illustrate, 13 patients admitted to the hospital

on the second day of the disease received serum. All of these patients had a crisis by the end of the fifth day and most of them before. The 9 patients who had equal hospital care but no serum admitted on the second day of the disease, continued to run a long course, with the crisis on the sixth to ninth day. Although the serum treated group has a greater number of patients with early hospital admissions, Chart 7 clearly indicates that this factor in itself does not tend to shorten the disease.

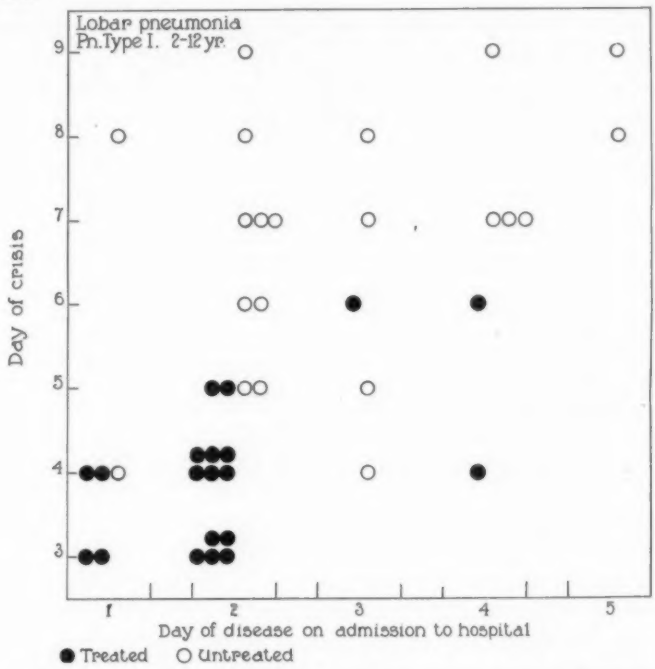

Chart 6.—Duration of the disease in treated and control groups with reference to period of hospitalization in pneumococcus Type I pneumonia. Each untreated patient is represented by an open circle; each treated patient, by a black circle. Although more serum treated patients were admitted to the hospital early in the disease, this factor alone does not shorten the disease. Patients untreated admitted on the same day of illness have a longer course.

Finally, only one patient of the 69 cases of lobar pneumonia treated with serum developed empyema. This seven-year-old child had 2 doses of pneumococcus Type V serum, a total of 10 c.c., 15,000 units on the fifth day of the disease and a crisis ensued. The empyema Type V was demonstrated after an afebrile period of three weeks. Of the 94 cases in the control group 4 developed empyema, two of the pneumococcus Type I origin, one pneumococcus Type XIV, and one Type V. A spread of the pneumonia to a new lobe was observed in 2 patients in the control group. There was no such complication in the treated group. No

patient receiving serum developed meningitis. Pneumococcus meningitis Type XIV was diagnosed in one patient in the control group; 3 infants had pneumococcus meningitis Type VI, all of whom died. One of these 3 infants received intravenous and intratheeal antipneumococcus serum. All 3 of these infants are excluded from the mortality rate.

The above facts tend to indicate that the complications following lobar pneumonia may be decreased by administration of antipneumococcus serum. Perhaps this difference is in part due to the fact that all the

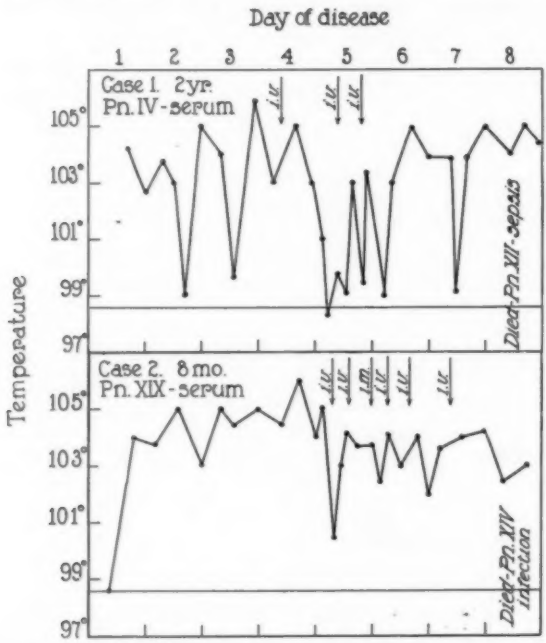

Chart 7.—Temperature curves of two patients failing to respond to serum. Case I is that of a two-year-old boy having Types IV and XII pneumococci in the laryngeal swabs. Serum for Type IV was given (no therapeutic serum for Type XII). Blood culture taken before treatment was positive for pneumococcus Type XII. Patient died with pneumococcus type XII sepsis and meningitis. Case 2 was treated with antipneumococcus Type XIX, the type obtained from 2 laryngeal swab cultures. No response to treatment. Pneumococcus Type XIV empyema developed. Probably an error in diagnosis of the etiologic agent was made. Pneumococcus Type XIX is most likely a nonpathogenic inhabitant of the throat.

serum treated group received serum relatively early in the course of their disease. It seems significant that the one case that developed empyema following serum therapy, received treatment late in the disease.

That pneumococci may be found in the throat of a normal person is a well-known fact. It becomes difficult at times to evaluate the presence of pneumococci in cultures from laryngeal swabs, as is illustrated in Case 2, Chart 7. Pneumococcus Type XIX was cultured from two laryngeal swabs and from the pus from the ear of a baby with lobar

pneumonia (confirmed at autopsy). Antipneumococcus serum Type XIX produced no appreciable improvement in the patient's condition. A pneumococcus Type XIV empyema, septicemia, and meningitis ensued, with subsequent death. In this patient, it seems reasonable to assert that the death was not due to failure of antipneumococcus serum but rather to a failure in the diagnosis of the etiologic agent.

Multiple pneumococcus infections are confusing also, but fortunately were infrequently found in the group reported. It was more commonly found in the group for which we have no serum. Case 1 (Chart 7) is that of a child having both Types IV and XII pneumococci in equal proportion in the culture from the laryngeal swab. A blood culture was taken before the administration of antipneumococcus serum Type IV. Therapeutic serum for Type XII was not available. The following day a report of the blood culture revealed only pneumococcus Type XII; a fatal meningitis developed and pneumococcus Type XII was cultured from the spinal fluid. Repeated laryngeal swabs revealed only Type XII pneumococcus.

Cultures of lung suction punctures might help in determining the true etiologic agent of the disease in such cases as the 2 cited above and also in patients with bronchopneumonia where the pneumococci, even when found frequently, may not be the true or sole etiologic agents of the disease. Pneumococci isolated from patients with bronchopneumonia are often associated with hemolytic streptococci or hemolytic staphylococci. On postmortem lung puncture cultures of patients with such mixed bacteriology, hemolytic staphylococci or hemolytic streptococci are usually found without pneumococci. Autopsy in many of these patients disclosed multiple abscesses in the lungs. Hence, it is suggested that even though pneumococci are found in the cultures from the laryngeal swabs of babies with bronchopneumonia, these organisms in many instances are probably not the etiologic agents of the disease. Blood cultures and cultures of other body fluids on a number of babies have been positive for streptococci even though pneumococci have been cultured from the swabs.

Although the laryngeal swab method of culture does lead to errors, as indicated, on the whole it is a more feasible method than lung suction puncture, and is satisfactory for the lobar pneumonia group in a very high percentage of cases.

Perhaps the more striking results of antipneumococcus Type I serum therapy is partly attributable to a greater accuracy in diagnosis of the type of infecting organism in patients with pneumococcus Type I pneumonia. During this investigation a moderate number of children and infants with acute pharyngitis and acute bronchitis were studied bacteriologically. Pneumococcus Type I was found only once in these cultures, whereas other types of pneumococcus were isolated rather com-

monly, particularly Type VI. Also, Type I is much less frequently found in healthy carriers than other types of pneumococci, as has been previously reported.

SUMMARY

Of the 207 patients with lobar and bronchopneumonia here reported 82 received antipneumococcus serum. The mortality rate for the combined group of lobar and bronchopneumonia was lower in patients receiving antipneumococcus serum. A much larger series than is here reported is necessary for the final determination of the value of a therapeutic agent upon mortality rate. The duration of lobar pneumonia in infants and children was definitely shortened in the serum group. Sixty per cent of all patients receiving serum had a crisis by the end of the fifth day as compared to 20 per cent for the control group. The most striking results were obtained with antipneumococcus Types I and XIV serums. The former is the predominant type for children and the latter for infants. Of the 109 children in the serum and control groups of lobar pneumonia 72 had pneumococcus Types I and XIV pneumonia, so that a large percentage of children (two to twelve years of age) can be given the benefit of these apparently effective serums.

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SYPHILIS AND PREMATURITY

With Special Reference to the Use of Stovarsol in Prophylactic and Curative Treatment of Congenital Syphilis

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SYPHILIS as a cause of prematurity has been noted by different observers in varying degrees. While Lyon and Bemis[1] found only one infant with syphilis out of 42 premature deaths, and Kehrer,[2] in a study of a large series of premature births, felt that syphilis played no important part, other authors have reported different observations. Crawford,[3] in a study of 231 premature infants at the Philadelphia Lying-In Hospital, found syphilis as the cause of 31 of the 91 cases in which a definite cause could be ascertained. McCord[4] found that in 243 autopsies of syphilitic babies, 11 per cent died prematurely. The same author,[5] in another series of 212 untreated syphilitic mothers, noted that 34 (16 per cent) premature babies were born alive, while 138 treated mothers were delivered of 27 (10.8 per cent) prematures. In a paper dealing with 200 autopsies on syphilitic fetuses, McCord[6] found that 139 (69.5 per cent) were prematurely born. Pye-Smith[7] found that of 222 deliveries among women with syphilis who had been treated antenatally, there were 38 premature births (17.29 per cent). Cruikshank[8] reported that the incidence of premature birth in women with a negative Wassermann reaction was 19.88 per cent, and that in women with a positive Wassermann reaction, the incidence was 32.54 per cent. He states that the result of prenatal treatment has been to reduce the occurrence of premature births to the normal. Funkhouser and Dickson[9] in a study of 73 negro newborn with strongly positive cord Wassermann reactions, found that 19 were prematurely born. Belding[10] states that syphilis tends to produce weak or premature infants. He found that the combined statistics of stillbirths and infants dying within two weeks after birth, show 1.47 times as many fatalities in the offspring of serum positive syphilitic mothers, as those of nonsyphilitic ones. Jeans[11] stated that prematurity and fetal deaths are two to three times as frequent in syphilitic as in nonsyphilitic families. Bartholomew[12] in a comparison of premature births from syphilitic and nonsyphilitic mothers, found 12 per cent in the former as compared to 7 per cent in the latter group. Wile and Shaw[13] noted that in 100 treated women, there were 7 prematures. Baumm[14] investigated 1,540 births and found that of 207 prematures syphilis caused 12.6 per cent. Coler[15] reviewed 9,955 births at Sloane

From the Premature Clinic of the Department of Pediatrics, Michael Reese Hospital.

Hospital for Women from 1922 to 1928, and noted that there were 355 cases of syphilis, of which 74, or 19.7 per cent, resulted in premature births. Hess[16] states that syphilis plays the leading rôle in infections which cause prematurity. Williams[17] found that 40 per cent of premature labors were due to syphilis. He states that Sentex in Pinard's clinic found syphilis in 42.7 per cent of 485 premature infants. Williams also wrote that syphilis should be suspected whenever a perfectly satisfactory explanation for the occurrence of prematurity cannot be adduced.

In any attempt to determine the causes of prematurity, it is extremely difficult, in many instances, to ascertain a definite cause. Knowing that syphilis is such a large factor in producing premature expulsion of the fetus, it is reasonable to feel that the presence of a positive serologic reaction for syphilis, in either parent, can explain, in the majority of cases, the reason for the prematurity. Undoubtedly some of these infants are not syphilitic, as any of the many other causes of prematurity may exist in the presence of syphilis, but from the standpoint of safety for the infant, it is wise to consider them as syphilitic.

From May 1, 1922, to January 1, 1933, there were 1,427 admissions of premature infants to the premature station in the Sarah Morris Hospital. Of these, 118 infants, or 8.27 per cent, were born of parents, either one or both of whom had a positive Wassermann or Kahn reaction, or definite clinical evidence of congenital syphilis. Several other reasons contributed either in whole or in part to prematurity in this group. Twin pregnancy occurred in 10 instances. Of these, 6 pairs are included; in 2 instances a single infant only was admitted, the other being of sufficient weight not to require hospital care; and in the last 2 instances, the second of each pair had been stillborn. Three mothers stated that they had heart disease; and one had influenza before delivering her child. Three mothers had toxemia of pregnancy, and labor was induced in 2 of them. One mother, in addition to a recent syphilitic infection, had a tuberculous hip of long duration. In this entire group only 2 private patients with syphilis are included, while approximately 20 per cent of all the 1,427 admissions were private patients.

Of the 118 infants in this group, there were 40 white and 78 negroes. One of the white infants was Chinese and 4 were Mexican. There were 54 male infants and 64 female. No reason can be advanced for the greater number of female infants, as one would expect approximately an even distribution in the sexes. Lawrence[18] reported the statistics of congenital syphilis in New York State (outside of New York City) in 1922, and found that of 225 cases, 113 were male and 112 were female. Bratusch-Marrain[19] found 60 per cent males of 435 cases of congenital syphilis.

The greater percentage of negro syphilities over white corresponds with the findings of all observers. Adair[20] reviewed comparative figures of syphilis in the white and colored races by different authors from which we quote: Gebhard reported 23.3 per cent syphilities among 1,224 colored pregnant women in New York City from 1917 to 1923. Stillians reported the following statistics from the Chicago Lying-In Hospital from 1917 to 1928: 6,954 pregnant women, mostly white, with an incidence of 6 per cent syphilis, 814 negroes with an incidence of 19.2 per cent. Williams, in Baltimore (1916-1919), found 2.48 per cent syphilis in white women, and 16.29 per cent in negro women.

TABLE I

RELATIONSHIP OF SYMPTOMS IN CHILD TO WASSERMANN REACTION OF PARENTS

PARENT	NUMBER OF INFANTS WITH SYMPTOMS OF SYPHILIS	NUMBER DIED IN HOSPITAL
Mother positive	21	6
Father positive	13	1
Mother and father positive	22	8
Mother and father negative	10	1
One negative, other unknown	4	2

TABLE II

RELATIONSHIP OF SYMPTOMLESS INFANTS TO WASSERMANN REACTIONS OF PARENTS

PARENT	NUMBER OF INFANTS	NUMBER DIED IN HOSPITAL
Mother positive	12	4
Father positive	18	5
Mother and father positive	10	4
Mother and father negative	6	0
One positive, other unknown	2	1

SEROLOGIC REACTIONS IN PARENTS

There were 110 families from which 118 infants were studied. Two mothers had 2 prematures at an interval of several years, and there were six twins. The Wassermann reaction in the mothers having two different prematures was the same each time, and neither had any treatment during either pregnancy. Both parents had a positive Wassermann or Kahn reaction in 34 instances. There were 33 mothers whose Wassermann reactions were positive, 18 of whose husbands had negative reactions. No test of the husband could be obtained in 15 instances. In 28 cases, the fathers' Wassermann reaction alone was positive. In 16 cases, both the father and mother had negative Wassermann reactions. Three mothers had negative reactions, with no report of the father's blood, and in 3 cases, neither parent was available for testing. No figures are available as to the duration of syphilitic infection in either parent.

HISTORY OF PREVIOUS PREGNANCIES

Twenty-nine of the mothers comprising this group were primiparas. Thirty-eight mothers gave a history of having had a total of 68 abortions. Eleven mothers had a total of 18 stillborn infants, and 12 others had previously borne 19 live premature infants. Six of these mothers had both abortions and stillbirths, or both abortions and previous prematures. Twenty-three mothers had had full-term infants, with the premature infants noted here as their first early termination of pregnancy.

TREATMENT OF MOTHERS

In general, the parents dealt with have been careless about their own treatment. Only 13 of the 97 mothers are known to have received antenatal treatment, and none of these received a sufficient amount as measured by present standards. Most mothers who went to prenatal clinics, visited them late in pregnancy, or immediately before delivery. Three of the infants born of this group of treated mothers died shortly after birth. In one of these infants, evidence of syphilis was found at autopsy.

TABLE III

SYMPTOMS*

Snuffles	26
Enlarged liver	11
Enlarged spleen	7
Desquamation	16
Indurated shiny palms and soles	10
Fissures	9
Rash	7
Mucous patches	1
Hemorrhage	9
Edema	4
General appearance	3
Adenopathy	2
Failure to gain	4

*The limited number of some of the manifestations recorded is in large part due to the fact that treatment was started immediately upon the report of positive serologic findings in one or both parents, even though the infants showed no signs of disease.

SYMPTOMS

Forty-eight infants did not have recognizable clinical signs of syphilis at any time. The symptoms noted in the remaining 70 are listed in Table III. Snuffles was the most frequently noted symptom, occurring in 26 infants. In 6 of these the discharge was bloody. One of these infants had a saddle nose deformity at birth. The usual time of appearance of snuffles was between the third and the fourteenth day. Characteristic desquamation involving the palms and soles, and the face, usually associated with other signs of syphilis, occurred in 15 infants. An enlarged liver was found in 11 babies, 7 of whom also had an enlarged spleen. Bleeding fissures about the nose, mouth, or anus occurred in 9 infants. Edema was present in 4 infants, involving par-

ticularly the lower limbs, abdomen, and scalp. An eruption was recorded in 10 cases, in 9 of which it was maculopapular in type; in the other one mucous patches occurred. Hemorrhage was present in 9 of these infants, accompanying unmistakable clinical signs of syphilis. The bleeding came from the rectum in 6 infants, the stomach in one, the vagina in one, and generalized ecchymosis occurred in one other.

RELATIONSHIP OF SYMPTOMS TO EARLY MORTALITY

Thirty-two of the premature infants died during their stay in the hospital, as listed in Tables I and II. Nine of these died within twenty-four hours after admission, which was usually a few hours after their birth.* Fourteen more died within two weeks, and the remaining 9 died before reaching the age of two months. Twenty-one infants had severe symptoms of syphilis shortly after birth, and of these, 18 died despite treatment. At postmortem, besides syphilitic changes observed, 2 had intracranial hemorrhage, 2 had bronchopneumonia, and 1 pneumococcic meningitis. Five infants who died weighed under one thousand grams. Of the 12 remaining infants, syphilitic changes were found in 5 at postmortem examination. Death was due in 5 instances to intracranial hemorrhage, in 2 to atelectasis, and in 2 to bronchopneumonia.

TREATMENT

Antisyphilitic treatment has been started in each infant routinely, upon the discovery of a positive Wassermann reaction in either parent. We feel that immediate treatment is justified for several reasons. First, a premature interruption of gestation in a syphilitic mother, even though she has been treated during pregnancy, is presumptive evidence of syphilis in the infants. Second, the earlier the treatment is instituted, the better the prognosis, except in cases of severe visceral syphilis, and third, as Wile and Shaw,[13] von Mettenheim,[21] and others have observed, it is becoming increasingly difficult to make a diagnosis of congenital syphilis early. These observers note that the picture of congenital syphilis has changed due to the treatment of mothers during pregnancy, so that very few of the infants show definite clinical evidence of the disease at birth. If these infants are allowed to go untreated, the disease may manifest itself as late as puberty, or even later.

Some American observers who begin treatment before the manifestation of symptoms are Atlee and Tyson,[22] who immediately treat all infants who have positive cord Wassermann reactions. McCord[23] also advocates this. Dunham[24] treats all offspring of mothers who have had an active or recent syphilitic infection and have not received

*Babies born at home or in hospitals other than Michael Reese, who need incubator care, are usually transported by special ambulance to the Sarah Morris Premature Station immediately after birth.

treatment antenatally. Wile and Shaw[13] believe that treatment should be instituted for all infants born of mothers with recent syphilis, even though treated during pregnancy. Kolmer[25] noted that it was advisable to regard every child of syphilitic parentage as infected, and administer antisyphilitic therapy even though the infant appears healthy and gives a negative Wassermann reaction, especially if either parent is uncured. Taylor[26] believes that all children born of syphilitic mothers treated during pregnancy, should be treated prophylactically for at least two years.

There are many European observers who believe that treatment should be given at birth to all offspring of syphilitic parents, regardless of the duration of the infection, and also to supplement the prenatal treatment given to the mother. Klaften[27] believes that every descendant from syphilitic parents should be subjected to prophylactic treatment. He noted that the mortality of infants with congenital syphilis was around 30 per cent, and that the mortality of those treated immediately was only 9.1 per cent. In view of this fact, he undertook preventive treatment in apparently healthy children born of syphilitic parents with a result that the mortality was reduced to 7.9 per cent. In another article, the same author[28] states that such authorities as Galliot, Jadassohn, Fischl, Finkelstein, Davidsohn, Pazzke, Pinard, Slavik, Noeggrath, Richter, Erich Müller, and others advocate the preventive treatment in newborn infants of syphilitic parents. Hoffman[29] believes that infants born of syphilitic mothers who have had a more or less energetic treatment during pregnancy, should be subjected to preventive therapy. He states that one must take exception to the rule, "no treatment without previous diagnosis."

Adams, in discussing a paper by Nabarro[30] stated that the battle in congenital syphilis is over in the first two or three months, and so institutes immediate treatment in all infants, even if their mothers had prenatal therapy. Marfan[31] suspects the presence of congenital syphilis in infants born of infected parents, even when no certain signs of the disease exist, and, even when the Wassermann reaction is negative, he would treat the infant as if the disease were certain. Pillsbury[32] believes that it is hardly logical to regard the almost certainly infected infant of a mother with early syphilis as cured by prenatal treatment. He notes that at the Welander homes, in the Scandinavian countries, where the long-continued observation of syphilitic mothers and children is unparalleled, it is the custom to continue treatment of the infant after birth, regardless of the absence of syphilitic symptoms. Scherber,[33] von den Steinen,[34] and Lereboullet,[35] also believe that all offspring of syphilitic parents should be subjected to prophylactic treatment.

While these observers are in the majority, there are many authorities who take an opposite stand. Boas[36] is strongly opposed to treat-

ing any child until the diagnosis is definitely established. Busehke and Gumpert[37] conclude that a child of syphilitic parents must by no means necessarily be infected, and they are very careful in the selection of children for prophylactic therapy. Hahn[38] institutes treatment in the offspring of syphilitic parents when their Wassermann reaction is negative only if they fail to gain properly in weight.

METHOD OF TREATMENT

Until the past twelve months, the routine treatment, either prophylactic or in the presence of symptoms, was to use mercury in the form of inunctions combined with oral administration of mercury and chalk, together with sulpharsphenamine injected intramuscularly. Mercury with chalk was started in the small dosage of one-eighth grain daily, because of the ease with which it causes diarrhea in very small infants. The dose was increased until infants one year old were receiving one grain three times daily. Inunctions of five grains of mercury ointment were used only during their stay in the hospital, and were given once daily for seven days, with seven days' rest. Sulpharsphenamine, in a dosage of 0.002 gram per kilogram of body weight, was injected once a week for six weeks with six weeks of rest, and this course was repeated twice during the first year. The mercury with chalk was given during the same time that the arsenical was being administered.

STOVARSOL THERAPY

During the past year, stovarsol has been the only drug employed in our clinic. Stovarsol, acetarsone, or acetylaminohydroxyphenylarsonic acid, known as "spirocid" in Germany, contains 27.1 to 27.4 per cent arsenic and is a white powder, odorless, with a slightly acid taste. It is manufactured in the form of 0.1 gram and 0.25 gram tablets. The 0.1 gram tablets are the only ones which were used in this study. A complete description of this drug is given by Maxwell and Glaser.[39]

The dosage given to infants as reported in the literature, varies markedly in amount. Thus, Soldin and Lesser[40] gave doses to infants in increasing amounts as follows:

¼ 0.25 gram tablet once daily for three days
¼ 0.25 gram tablet twice daily for three days
¼ 0.25 gram tablet 3 times daily for three days
½ 0.25 gram tablet twice daily for three months, and from then on
½ 0.25 gram tablet 3 or 4 times daily, until a minimum total dosage of 35 grams had been administered

Tuscherer,[41] working in the University clinic in Berlin, also used large doses both in infants and older children. His regimen was to give the following:

¼ 0.25 gram tablet once daily for three days
¼ 0.25 gram tablet 2 times daily for three days

¼ 0.25 gram tablet 3 times daily for three days
¼ 0.25 gram tablet 4 times daily for three days
½ 0.25 gram tablet 4 times daily for three days
1 0.25 gram tablet 2 times daily for three days
1 0.25 gram tablet 3 times daily until a total dosage of 21 grams in forty-one days was given. At least one more similar course was repeated, even though the infants had a negative Wassermann reaction at the end of treatment.

Klaften gives newborn infants one-half of a 0.25 gram tablet the first day after birth. During the first week he gives three and one-half tablets combined with mercury. The whole course of prophylactic treatment thus instituted lasts eleven or twelve weeks, during which time fifteen grams, or sixty 0.25 gram tablets are administered. In premature infants, however, he gives smaller quantities. One-quarter of a 0.25 gram tablet is given the first day of the first week of treatment, and half a tablet the remaining six days. In the second week, one-half tablet twice daily is given, and without further increase a total of four to six grams is administered.

Smaller doses are advocated by some. Oppenheim and Fessler[42] give a daily dose of 0.01 to 0.03 gram to newborn infants, and to nurslings up to six months 0.05 to 0.12 gram daily. Courtin,[43] quoting Danzer, reports that his system is to give a daily dose of 0.01 gram for three months, giving a total dose of only four to five grams of the drug. Krösl[44] recommends a dose of 0.02 gram per kilogram of body weight for four consecutive days each week for six or eight weeks. Other observers, Erich Müller,[45] von den Steinen,[34] Wegner,[46] and Bleschmann[47] also believe that a rest should be given after several days of treatment to allow the patient to eliminate the arsenic taken.

Scherber[33] gives three 0.1 gram tablets daily and increases the dosage to six tablets daily. He obtains the permissible total dosage by dividing the weight of the child in kilograms by four. Thus, a ten-kilogram infant would receive 2.5 grams in a total course.

Bratusch-Marrain[48] recommends that the drug be given in relation to the body weight of the infant. He gives the following:

0.005 gram per kilogram daily for 1st week
0.010 gram per kilogram daily for 2nd week
0.015 gram per kilogram daily for 3rd week
0.02 gram per kilogram daily for 4th week
and continues at this dosage for five more weeks, after which a rest period of six weeks is instituted.

Since extreme care in administering arsenic to young infants is always necessary, it appears that this type of dose is advisable. I have used this system advised by Bratusch-Marrain,[48] after seeing it used

so successfully by Abt and Traisman[64] at Northwestern University Clinic. This method has also yielded excellent results when used by Rosenbaum.[50]

Three such courses are given the first year, and are continued at least one more year. Wassermann tests are made at the end of each rest period.

Thirty-two infants have been treated with stovarsol. Of these, 8 have had this drug alone, 7 have had mercury in combination with stovarsol, and the remaining 17 have had previous courses of mercury and sulpharsphenamine.*

EFFECT OF STOVARSOL ON SYMPTOMS AND ON WASSERMANN REACTIONS

In 9 infants who had snuffles the condition cleared up in from four to eight weeks. Five of these infants received mercury and chalk together with stovarsol, with no more rapid change in symptoms than those on stovarsol alone. Five infants had splenic and hepatic enlargement. In 3 of these the liver and spleen were no longer palpable at the end of one course of therapy; in the other 2, the liver was no longer palpable at the end of two courses, but the spleen was still enlarged. It was, however, in each case, smaller than when originally noted, and much less firm in consistency.

Six of the 17 infants who received stovarsol after having previously been treated with mercury and sulpharsphenamine, were under one year of age. All of these infants were clinically and serologically negative when stovarsol treatment was begun. Stovarsol was used simply to complete an adequate amount of therapy.

The blood Wassermann and Kahn reactions have been negative after one course of therapy in all the infants treated with stovarsol, or with mercury and stovarsol, and all have remained so. Twelve infants have had 3 negative reactions when taken at the end of each rest period, and 3 have had two such negative reactions. One infant who had a two-plus Wassermann and Kahn reaction following the use of one course of mercury and sulpharsphenamine, had a reversal of the reaction following the added use of one course of stovarsol. The reaction remained negative on two further examinations.

A favorable effect of stovarsol on the Wassermann reaction in infants with syphilis has been reported by all authors. Abt and Traisman[49] had positive Wassermann reactions reversed after treatment in 14 out of 18 infants. Rosenbaum[50] reversed the positive Wassermann reactions in all of 9 children who had treatment begun during their first year. Maxwell and Glaser[39] treated 10 infants under one year, 4 of whom had negative Wassermann reactions at the start that remained negative, while 6 others with positive Wassermann reactions,

*Infants are brought to the clinic each week and only enough of the drug to last one week is given. It is advised that the drug be dissolved in water or weak tea and given thirty minutes before a feeding.

became negative after treatment. Von den Steinen[34] produced a negative reaction in 8 of 9 infants treated. Nedelmann[51] treated 18 infants, with a reversal of the Wassermann reaction in 17 after one course of therapy, the other becoming negative after a second course. Fourteen of these were reexamined in from three to twenty-six months and all were serologically negative and free from relapses. Soldin and Lesser[40] reported 13 infants who became seronegative after treatment. In 7 cases a total of fifteen grams was used; in 2 cases twenty grams; in 3 cases twenty-five grams, and in 1 case fifty grams were necessary. Krombach[52] reported that 13 of 14 infants treated became negative after one course. Oppenheim and Fessler, Tuscherer and others have reported good results.

EFFECT OF SULPHARSPHENAMINE AND MERCURY ON SYMPTOMS AND WASSERMANN REACTIONS

The clinical symptoms of syphilis which appeared during the early weeks of life in the hospital in 31 infants treated with mercury and sulpharsphenamine were cleared up as follows: snuffles disappeared in from three to eight weeks; skin manifestations, except fissures, disappeared in from one to two weeks; 5 infants with enlarged livers or spleens, or both, still showed evidence of enlargement at the end of one course of treatment, but this disappeared by the end of the second course.

It is unfortunate that Wassermann tests were not taken on these infants before treatment was begun. Since, with very few exceptions, these children were born in homes, no cord blood or placentas were available to us for study. Of the 43 infants who had sulpharsphenamine and mercury therapy, the Wassermann and Kahn reactions were negative in 41, and remained so throughout the period that they were watched. Twenty-six infants treated only in the hospital were lost track of on discharge, as well as 2 private cases.

One infant treated from birth on, had a negative Wassermann reaction at the end of one course of therapy, which became strongly positive after the second course was given. This child died later of arsenic poisoning.

One other child who had a weakly positive Wassermann reaction after one course of treatment, had this reaction reversed by one succeeding course of stovarsol, as before noted.

EFFECT OF EARLY TREATMENT ON MORBIDITY AND MORTALITY

Congenital syphilis decreases the defensive mechanism of the infant, and frequent secondary infections occur. Lewin[53] states that most syphilitic children die of secondary infections. Fürst,[54] in a study of 702 children with congenital syphilis, noted that the total mortality was over 50 per cent with the causes of death as follows: pneumonia, 110 cases; meningitis, 5 cases; debility, 6 cases; enteritis, 37 cases; and mis-

cellaneous and unknown, 161 cases. Husten[55] investigated the fate of 39 cases of congenital syphilis and found that one-half died of intercurrent infections, with only 16 living at the time of his study. Antoniewicz[56] reported that 15 of 46 children, or 32.4 per cent, treated after manifest symptoms occurred, died (10 before reaching the age of one year), while in a group of 36 infants born of syphilitic parents and treated prophylactically from birth on, only 6 per cent died, and all of these were over one year of age. Lange[57] observed 100 syphilitic infants for ten years. Sixty-seven of these died, 52 from respiratory and intestinal diseases. Ten of the infants were premature, and only one survived. He noted that even though symptoms of syphilis had disappeared after treatment, the children withstood infections poorly. White and Veeder[58] reported the results of treatment of 197 cases, less than two years of age. Sixty died, or a mortality of 30.1 per cent. Fourteen of the infants treated were premature, and 6, or 43 per cent, of them died.

Forty of the 58 infants followed in the clinic have had infections of varying degrees of severity. All of these infants have had one or more attacks of nasopharyngitis, and 15 have had otitis media. Bronchopneumonia occurred in 10 infants, bronchitis in 4, cervical adenitis in 3, pyelitis in 1, and gastroenteritis in 6.

Premature infants are naturally more susceptible to secondary infections because of their size and lack of immunity to disease, so that the infections that occurred in this group cannot necessarily be blamed on a lowered defense mechanism due to syphilis. The hygienic surroundings of this group of infants at home have been very inferior, and it is probable that exposure to respiratory infections, in particular, has been frequent.

Mild symptoms of rickets occur with frequency in many premature infants even with adequate prophylactic therapy. Four of this group developed moderately severe rickets. Three of these infants were negroes.

One infant in this group had hydrocephalus, and one had spina bifida occulta. Otherwise, no abnormalities have been discovered.

At the present time there are under observation in the premature clinic 38 of these children. Twelve of them are over two years of age, 11 are between one and two years, and 15 are under one year. Fifteen others were treated for at least two years, but have since been lost track of. Two others over two years of age are now in institutions. During the time that the infants were under clinic care, only 2, or 3.44 per cent, died. One of these, the infant before mentioned as having a strongly positive Wassermann reaction after treatment, died at the age of sixteen months from arsenic poisoning, following an injection of sulpharsphenamine in the third series of treatment. The twin sister of this child died a short time afterward at home from what was probably bronchopneumonia.

TABLE IV

INFLUENCE OF TREATMENT ON WEIGHT

	NUMBER OF INFANTS	AVERAGE WEIGHT AT SIX MONTHS	AVERAGE WEIGHT AT TWELVE MONTHS
Normal	200	4025	6100
Sulpharsphenamine	43	3760	6035
Stovarsol	8	3780	6645

Improvement in general body tone and weight is always noted in syphilitic infants while under treatment. In Table IV the average gains made during six months and one year are noted. The average listed under the heading "normal" was obtained from all of the nonsyphilitic infants brought to the clinic during the past two years. Gains during the first six months are very much alike in each group, while the average gain for the whole year made by the infants who received stovarsol is over 500 grams greater than the gain for the nonsyphilitic group for the same length of time. It must be remembered that this group treated with stovarsol is much smaller in number than either of the other groups. Improvement was often noted as soon as stovarsol was started, while these same infants did not do particularly well during the six-week rest periods. Increase in appetite and activity was frequently reported by the mothers.

Tezner,[59] noting the marked improvement in treated syphilitic infants, advocated the use of stovarsol in dystrophic and poorly thriving nurslings. Lesser and Soldin[40] especially emphasized the gain in weight of syphilitic infants treated with stovarsol and traced this to the favorable effect of the arsenic. Von Mettenheim[21] states that besides the specific effect of stovarsol on syphilitic lesions, the drug has a tonic effect. He found in the 18 infants which he treated, that the weight and general health improved, and the hemoglobin rose rapidly. Niederwieser[60] used stovarsol in nonsyphilitic infants suffering from anorexia and loss of weight and reported good results. Bratusch-Marrain[48] emphasized the good effects of spirocid treatment upon the physical development of those infants so treated. Juarros and Galarreta,[61] in treating 40 older children with spirocid, reported that the most constant effect of the drug was an increase, sometimes very accentuated, in weight and height. Tuscherer[41] observed that children with congenital syphilis, except those with severe visceral lesions, improve physically during the course of treatment with stovarsol, which he attributes to the arsenic. He found that the weight curves resembled those of healthy infants.

TOXIC SYMPTOMS RESULTING FROM STOVARSOL

All observers note that toxic effects from arsenic are less marked in infants than in older children. Soldin and Lesser[40] reported mild

Herxheimer reactions in infants, as did Krombach.[52] After the drug was discontinued for some time, it was well tolerated again.

Toxic symptoms resulting from stovarsol or spirocid occur frequently, but they are usually mild. In infants the most frequent toxic manifestations are diarrhea, vomiting, cutaneous symptoms, and fever. Diarrhea has been noted by many observers. Krombach[52] reported occasional attacks in infants that she treated. Guillemot[62] noted that slight digestive disturbances occurred frequently. Huber[63] reported that 3 infants out of 16 treated developed diarrhea. Bratusch-Marrain stated that some infants receiving his customary dosage showed frequent and thin stools, but these never took on an alarming character, and always disappeared rapidly after the drug was discontinued. Abt and Traisman,[64] and Maxwell and Glaser[39] have noted mild diarrheas in some of the infants they treated.

Exanthems of a morbilliform and scarletiniform type have been frequently noted as have urticarial and bullous lesions.

Transient albuminuria has been found by Abt and Traisman,[64] and Maxwell and Glaser.[39] The latter authors treated 2 infants who developed a generalized flaccidity, one of whom died.

In the 32 premature infants that I have treated with stovarsol, there have been three who developed a mild diarrhea. In each case this has occurred during the fifth or sixth week of therapy, after a total dosage of from 2.5 to 3 grams of the drug. The looseness of the stools ceased shortly after the withdrawal of the medication, and treatment was started again after a lapse of one week, with no further upset.

Two infants developed an urticarial rash on the extremities, which disappeared within one week after temporarily discontinuing the drug.

One infant, twenty-four days old, developed a diffuse redness of the skin over the face, trunk, and extremities, which was followed by a generalized desquamation. No constitutional symptoms accompanied this, and the infant gained four hundred grams in the two weeks that the desquamation continued.

In most cases it has been difficult for the mothers to obtain regular specimens of urine from the infants treated. A trace of albumin was noted transiently in 11 of 20 infants and children whose urine was examined. No abnormal microscopic findings have accompanied this albumin, and it has not been considered a contraindication to the continued use of the drug.

COMMENT

The earlier antisyphilitic treatment is started in congenital syphilis, the better the chances for a normal infant and a serologic cure. Many infants who have congenital syphilis do not show signs early, and often the early signs are so mild that it is difficult to interpret them. An extensive review of the literature reveals that it is considered

wise, particularly abroad, to subject all offspring of syphilitic parents to prophylactic therapy, especially where there has been a recent infection, and where mothers did not have sufficient antenatal treatment. It is difficult and probably wrong to label a child from such a parent as syphilitic without clinical or laboratory evidence of the disease, but if one is to wait for this evidence, much valuable time may be lost, resulting in the failure to secure as good results as might have been obtained through early treatment. Where treatment involves the use of intramuscular injections, it is impossible not to brand the child as syphilitic, while if a peroral form of treatment can be used, it is simple to advise and employ this form of therapy without stigmatizing the child. It is extremely difficult to have patients return regularly for injection therapy, while no lack of cooperation has been evidenced with the simple dispensing of the stovarsol tablets. When the parents can actually see an improvement in the infant as far as gains in weight and body turgor are concerned, occurring during such periods of therapy, they are usually anxious to come to clinic regularly for the medication.

While in all probability many of this group of infants did not have syphilis, the mortality of only 3.44 per cent is evidence that the prophylactic treatment has been of great value. The Wassermann reaction in all infants and children so treated has been negative, and no later signs of syphilis have as yet occurred.

SUMMARY

1. At least two years of treatment, either prophylactic or curative, is advised for all premature offspring of syphilitic parents.

2. Fifty-eight infants have been treated prophylactically or curatively for congenital syphilis. Of these, 8 have received stovarsol alone, 7 have had mercury and chalk in conjunction with stovarsol, and 43 have had mercury and sulpharsphenamine. Of the latter group, 17 have had stovarsol in their second year of treatment.

3. While no attempt is made to compare the results obtained by either form of therapy, stovarsol by mouth is advised because of its ease of administration, and the resulting cooperation of the parents.

4. No serious toxic symptoms have resulted from the use of stovarsol.

5. Early treatment has resulted in a known mortality of only 3.44 per cent of the infants discharged from the premature station to their homes, 27.9 per cent of the total 118 having died during their original admission to the hospital.

The stovarsol used in this study was furnished through the courtesy of Merck & Co.

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GROWTH PROBLEMS

II. Basal Metabolic Rate Variations in Relation to Body Build Adolescence and Allergy in Children

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A STUDY of 1,334 basal rate determinations on 680 normal children shows every gradation from high to low rate. The rates plotted follow a typical normal distribution curve similar to the distribution curves of any other biologic data in a large series.

Symmetrical variation above and below the average is seen in the normal distribution curve of any trait, the majority of cases being classified *normal*, whether the data are height or oxygen consumption or introversion. It is necessary to plot the entire curve of distribution in order to recognize degrees of deviation, and the total curve should be kept in mind in diagnosing *normal* functions for any individual.

BODY BUILD FACTOR IN BASAL METABOLISM

Parallel studies of basal metabolic rate and body build in 415 children[1] showed a definite relationship between thyroid activity and type of body build. High basal rates were the rule for the slender-built and low basal rates for the broad-built. Oxygen consumption was compared with body build by means of the Pearson correlation coefficients. The relationship between percentage deviations from average calories per kilogram body weight per hour, and from average width-length index of build for age and sex were as follows:

177 boys	Ages 3-17 years	r* = −0.196	±0.049
238 girls	Ages 3-17 years	r = −0.262	±0.041

These negative correlations showed that degrees of slenderness below average of body build were related to degrees of increase above average in oxygen absorption in this group of 415 children. In other words, the difference in relative width of the body (measured by the width-length index) seemed to be a determining factor in oxygen absorption when both were on a unit basis.

Our approach in the present study, being medical and not surgical, has employed the basal metabolic rate as its method for recognizing levels of glandular function. Consequently, the classification of the children has been in terms of basal metabolic rate variations. Recognizable pathologic thyroid abnormalities have been excluded from this study.

*r equals the Pearson coefficient of correlation.

If biopsy were feasible we wonder if even these remaining thyroids might not show histologic staining differences consistent with varying degrees of secretory activity. We have considered this series to represent hypo- and hyperfunction without hypo- and hyperplasia. We have not seen any progressive tendency toward the pathologic entities.

What determines the levels of glandular activity is debatable, although suspicion falls strongly on inheritance. Physical type, however, seems to be almost invariably a consequence of glandular state.

The groups called linear and lateral undoubtedly are to be associated with thyroid hyper- and hypofunctions, respectively, and the body changes induced by extreme gross pathologic thyroid states are unquestioned and diagnostic.

Our basal rates were referred to the Benedict-Talbot standard. They were done after one-half hour rest, in the postabsorptive state, and represent at least two consecutive determinations that check.

HIGH BASAL METABOLIC RATES IN SLENDER CHILDREN

One hundred and ten of our 680 children had basal metabolic rates of 20 per cent plus and over, but exhibited none of the cardinal toxic

TABLE I

HIGH BASAL METABOLIC RATES IN SLENDER-BUILT CHILDREN

CASE NO.	AGE	SEX	W-L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B. M. R. PER CENT	CALORIES PER HOUR
81	4	F		−30.0	+54.0	39.0
5a	4	F		− 7.4	+42.0	
564	5	F	−7	−21.0	+28.8	39.7
141	6	M	−1	− 3.9	+29.0	49.0
558	6	M	−6	−15.3	+29.0	46.3
	6			−11.7	+25.1	46.7
491	6	M		−18.0	+31.0	50.7
443	6	M		− 3.0	+38.4	51.5
155	8	M	−5	−12.6	+33.0	47.5
406	8	F		−21.0	+36.8	50.1
	9			−13.5	+25.7	51.7
72	8	F	+3	− 8.7	+45.1	49.2
160a	8	M		− 9.5	+37.3	
340a	9	F	−5	− 1.8	+44.0	52.4
49	9	F	−1	−15.0	+64.3	57.5
87a	10	F	−3	− 5.9	+23.0	52.3
322	12	F		−16.4	+25.0	63.8
412	16	F	−1	−13.3	+24.0	68.5

The Width-Length Index variation shows relative breadth, or percentage broader or narrower than average, for the age, sex, group.

Variation from average weight shows the percentage underweight referred to the Baldwin-Wood standard.

B.M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot scale.

signs of hyperthyroidism, such as tremor, exophthalmus and other eye signs, hyperhidrosis, and polyphagia. They were, however, high-strung, easily fatigued children, and often had rapid pulses. The

following 18 cases (see Table I) illustrate this group. They occurred at all ages in both sexes. They were slender-built and underweight when compared with the height-weight-age table averages. But when allowance was made for body build, measured by the width-length index, their nutrition as a whole was good. They were often over-ambitious and undertook many outside activities in addition to their school work.

These children improved clinically when put on a rest regime, and when they were given iodine in the form of Lugol's solution. Their psychologic improvement was often spectacular.

THE AGE FACTOR IN BASAL METABOLISM

In a previous paper[2] we have pointed out the fact that young children had higher basal rates than older children in our series, and that, in general, the younger the child, the higher the rate.

Because the mean basal metabolic rates in our series were so high at the younger age levels, we have suggested a correction factor of minus 11.5 per cent in interpreting basal rates for preadolescent children. Our averages were as follows:

169 girls	Ages 3- 9 years	plus 10.0%
140 boys	Ages 3- 9 years	plus 14.0%
134 girls	Ages 10-18 years	plus 2.5%
130 boys	Ages 10-18 years	plus 0.5%

Various other physiologic data tend to emphasize the reasonableness of these high basal metabolic rates in young children. For instance, it has been established that young children normally have more rapid pulse rates than older children, and that the rate is progressively higher the younger the child.

To quote Abt's *System of Pediatrics*, Vol. IV, page 220, "Average figures compiled from many observations at the same ages tend to show that a progressive decrease in heart rate occurs until adult life is reached." His table of maximum and minimum heart rates at different ages is as follows:

AGE YEARS	MAXIMUM FREQUENCY	MINIMUM FREQUENCY
0–1	134.0	101
1–2	110.6	84
2–3	108.0	84
4–5	103.0	80
5–6	98.0	70
6–7	92.1	72
7–8	94.9	72
8–9	88.8	72
9–10	91.8	68
10–11	87.9	56
11–12	89.9	60
12–13	87.9	67
13–14	86.8	66

"Statistics also show that there is a relation between the height and weight and the heart rate in children of the same age, in the sense that the heart rate tends to be slower in children of larger stature." This is shown in the accompanying table by Volkmann.

RELATION OF HEART RATE TO BODY LENGTH AT DIFFERENT AGES (VOLKMANN)

AGE	SMALL CHILDREN	LARGE CHILDREN
1	146.5	123.1
2	124.0	111.0
3	113.2	104.3
4	111.7	110.2
5	106.0	102.3
6	102.5	99.9
7	101.0	93.8
8	97.0	98.0
9	90.0	89.0
10	93.0	88.0
11	88.5	85.9
12	91.3	81.0
13	87.6	81.0
14	89.5	89.3
15	81.0	81.0

Recent work[3] indicates that the normal body temperature is higher for young children than for adults. Dr. Stolz and Miss Ludwig at the Institute of Child Welfare, University of California, have studied variations in body temperature in healthy pre-school children. Rectal temperatures were taken at nine and eleven o'clock in the morning and at one and three o'clock in the afternoon each day on 18 children. They reported that each child had his own range of temperature. In one child the average of all temperature readings was as high as 100° F., and another as low as 99.2° F. The average for the total series of records was 99.5° F., which is distinctly higher than the rectal temperature of 98.96° F., which Howell reports as normal for healthy adults.

Jenkins[4] reported mean body temperatures taken at the time of basal metabolic rate determinations for 846 men to be 97.7° F., and for 2,408 women to be 98.1° F. These were mouth temperatures, and are a little lower than Howell's[5] figures.

Jenkins' material indicates that a "rise of one degree Fahrenheit is equal to a rise in the basal rate of seven per cent in the case of men, or five per cent in the case of women. One degree Centigrade is the equivalent of twelve per cent for the men and nine per cent for the women." Dubois reports 7.2 per cent for each degree Fahrenheit or 13 per cent for each degree Centigrade.

Because the pulse rate is normally higher, and the body temperature is normally higher, at the younger age levels, both of these facts seem logically in keeping with higher basal metabolic rates in young children, since rapid pulse and wasteful rate of oxidation are associated with an overactive thyroid gland.

Our findings would tend to agree in theory with Jenkins' basal pulse complex and with the prediction formula of Read,[6] although to date we have not made use of these methods.

The clinical application of these facts may be helpful in understanding a certain type of persistent low-grade febrile state which often reaches the pediatrician. After negative physical examinations, negative intradermal tuberculin tests, and negative roentgen studies, children with this complaint frequently remain under suspicion of obscure infection, usually pulmonary or hilar.

Several observers[7] have reported a prepuberal rise in the basal metabolic rate. Inasmuch as our figures show basal rates much higher for preadolescent than for adolescent children, we wonder if the apparent prepuberal rise is not because the first observations were made at ages nine to ten instead of at ages five to six years. The averages of 1,334 first satisfactory basal rate determinations by age and sex for our 680 children are as follows:

AGES	BOYS		GIRLS	
	NUMBER CASES	AVERAGE BASAL METABOLIC RATE	NUMBER CASES	AVERAGE BASAL METABOLIC RATE
3–5	31	plus 16.91%	35	plus 11.42%
6–9	135	plus 10.71%	162	plus 8.53%
10–17	141	plus 0.25%	176	plus 2.58%

It will be seen that there is not only a prepuberal rise, but that there is a consistent and continual rise as the age level recedes to early childhood.

Consequently, it may be stated more accurately that the basal metabolic rate decreases regularly from early childhood to adolescence.

BASAL METABOLIC RATE VARIATIONS DURING ADOLESCENCE

The so-called distorted energy requirement of adolescent children is illustrated in the widely variant basal metabolic rates obtained during this period. The unusual activity and demands made by rapid growth is offered as explanation. Table V shows a serial study of basal metabolic rates on 26 of our adolescent children. Wide fluctuations in rate and rapid swinging from plus to minus or minus to plus were characteristic of this group.

Blunt, Tilt, McLaughlin, and Gunn[8] studied 46 girls aged nine to eighteen years at yearly intervals. They state that neither the average figures for the different ages, nor the variation in their few individual girls showed any effect of puberty.

Gardiner and Brett[9] in a study of adolescent goiter compared physical measurements of one hundred cases of colloid goiter with average standards for height and weight. They reported that a large majority

TABLE II

WIDE FLUCTUATIONS IN BASAL RATES DURING ADOLESCENCE ILLUSTRATE THE "DISTORTED ENERGY" REQUIREMENT

CASE NO.	AGE	SEX	W-L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B. M. R. PER CENT	CALORIES PER HOUR
290a	10–9	M	–6	–11.0	+18.0	53.6
	11–0			–10.0	+25.9	59.4
	11–3			–11.3	+ 4.5	48.6
	11–6			–10.8	+11.6	53.7
108	11–5	M	+1	– 9.3	+ 2.7	56.0
	11–8			–12.0	–21.0	45.7
	11–9			–12.0	+13.1	47.0
	11–11			–15.6	0.0	54.7
	12–6			–16.3	+21.9	68.4
	12–8			–15.7	+15.7	64.1
	13–0			–17.0	+ 2.0	59.6
	13–5			–11.4	+11.6	
553	11–9	M	+2	+13.7	+23.3	66.9
	12–4			+10.4	– 9.0	51.3
	12–7			+ 1.8	–10.5	50.6
392	10–4	M	+6	+31.0	–16.4	46.0
	10–7			+10.4	0.0	51.4
	12–8			+22.7	– 2.0	66.9
	12–10			+23.5	+15.5	57.3
437	12–0	M	+6	+11.1	–14.2	46.5
	12–6			0.0	– 7.2	51.5
	13–0			0.0	–21.0	45.4
	13–6			+ 4.5	– 6.4	57.8
463	11–0	M	–1	+14.8	–10.2	48.0
	11–4			+21.5	–12.0	48.1
	12–0			+21.2	+ 2.7	59.6
	12–4			+30.0	–10.7	58.9
546	9–5	M	–1	–12.5	–16.9	30.8
	9–8			–11.1	+ 5.5	45.9
	9–11			– 9.2	– 5.7	42.9
	10–8			– 4.0	+23.8	60.7
	11–1			– 3.2	+ 7.2	53.2
84	9–9	F	–7	–25.0	+21.7	51.6
	10–0			– 7.2	+ 4.0	50.6
	10–1			– 7.7	– 4.7	46.0
	10–4			– 5.1	–12.8	43.9
	11–4			–16.6	+25.0	66.4
	11–7			–11.0	+ 5.5	64.3
	11–10			–14.0	+18.3	54.6
419	9–8	F	+2	+12.1	0.0	51.0
	10–2			+10.9	– 3.5	49.0
	10–6			+ 7.0	–18.0	41.8
	11–0			+ 5.0	0.0	50.8
	11–7			+ 9.6	+16.9	60.7
	12–0			+15.6	+11.8	58.4
410	11–1	F	+3	+40.0	– 8.2	48.4
	11–7			+13.6	+ 1.0	52.3
	12–7			+24.5	+ 7.1	56.9

The Width-Length Index variation shows relative body width, or percentage broader or narrower than average, for the age, sex, group.

Variation from average weight shows the percentage overweight or underweight referred to the Baldwin-Wood height-weight table.

B.M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot scale.

Benedict-Hendry-Baker and Aub Dubois standards were used for a few cases.

TABLE II—CONT'D

CASE NO.	AGE	SEX	W-L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B. M. R. PER CENT	CALORIES PER HOUR
547	11–	F	–6	– 5.4	–20.8	34.4
	12–			+ 9.1	+ 9.1	55.8
	13–			0.0	+10.2	56.2
151	13–5	M	+5	+14.1	+ 5.3	72.2
	13–7			+10.4	+ 9.5	75.8
	13–9			+12.4	– 7.8	63.7
	14–3			+10.0	– 7.2	65.3
337	12–10	M	–8	–14.1	–26.7	40.0
	13–2			0.0	–29.0	43.0
	13–8			– 9.0	–15.8	50.4
	14–2			–13.7	–10.8	54.5
202	12–2	M	–2	– 4.7	–11.8	47.6
	12–8			– 3.0	–13.1	48.1
	13–0			– 7.6	+13.9	64.6
	13–6			– 5.0	–13.0	52.6
	14–0			– 2.3	0.0	63.7
389	11–10	M	+1	–10.0	+11.8	60.3
	12–1			– 3.6	+ 9.9	60.2
	12–3			– 3.0	+ 5.9	60.2
218	12–6	M	+3	+13.8	+ 1.3	52.2
	13–0			+ 8.0	–12.8	47.4
	13–2			+ 8.0	–18.0	57.3
	14–5			+12.7	+ 2.6	61.6
246	10–2	F	–2	+ 9.0	– 5.0	64.4
	10–8			+ 2.0	+23.0	48.4
	11–0			– 6.6	+ 2.3	53.2
	11–11			– 8.6	– 5.8	
188	11–3	F	+2	– 8.6	+10.1	45.3
	11–7			– 7.6	+11.3	47.1
	12–9			– 3.6	–10.5	38.1
56	10–3	F		+34.0	–22.0	
	11–4			+ 9.0	–23.0	
	12–0			+ 6.0	+ 2.0	54.4
	12–1			+10.8	+ 3.2	55.5
253	10	F	+5	+21.8	+27.7	67.2
	11			+30.0	+18.3	63.3
	12			+31.5	– 9.2	79.7
	13			+22.8	–19.0	79.3
326	10–8	F	+5	+18.0	+18.0	53.6
	11–7			0.0	– 9.5	43.7
	13–1			– 5.8	+15.1	57.7
332	10–8	F	+16	+23.0	–27.0	
	11–0			+23.0	–19.0	
	11–6			+27.1	+34.6	71.9
	11–9			+24.5	+ 9.6	58.8
	12–6			+23.8	–18.4	51.0
	13–0			+ 8.0	+16.0	61.8
	13–5			+ 4.4	– 2.8	51.6
364	11–5	F	+5	+ 5.2	+ 5.2	54.4
	12–0			+ 3.7	+ 8.8	46.8
	14–1			– 5.0	+26.9	66.7
	14–3			– 5.9	+11.0	57.8

TABLE II—CONT'D

CASE NO.	AGE	SEX	W-L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B. M. R. PER CENT	CALORIES PER HOUR
372	10–2	F	–1	–11.1	–14.8	36.2
	10–9			– 3.8	+ 9.6	51.8
	11–0			– 2.1	–10.3	43.3
	11–3			– 0.3	–12.9	43.7
	11–6				– 4.5	
181	10–2	F	–6	– 8.0	– 3.3	43.9
	10–9			– 9.0	+25.4	59.3
	11–4			– 5.7	+30.2	66.7
445	12–	F	–12	–17.2	+ 9.3	51.5
	13–			–12.5	+33.5	68.4
	13–			– 9.0	+ 7.1	55.1
	14–			–11.5	+28.1	65.9

of children with goiter were above average height for their age. Their hyperthyroid patients were below average weight for age and height. Their hypothyroid patients were above average weight for age and height.

Stocks, Stocks, and Karn[10] reported a similar finding with a possible explanation as follows: "Goiter tends to appear more readily or to become more pronounced in relation to the child's size (in girls whose heights are above average for their ages), or girls whose thyroids enlarge about puberty tend in consequence to grow more rapidly in height." The authors incline toward the first explanation.

Holmgren[11] in 1910 studied the growth spurt at puberty. He thought that rapid growth in height at the time of puberty was likely to produce a hyperthyroid reaction. In 1929 Thomas[12] stated that this conjunction of high metabolism with hyperthyroidism and rapid growth indicated that the thyroid hormone which stimulates metabolism was identical with the growth-accelerating hormone of the thyroid.

FACTORS IN LOW BASAL METABOLISM

Fasting has been shown to lower the basal metabolic rate. Talbot's[13] study of fasting in cases of idiopathic convulsions in children in 1925, demonstrated definite reduction in metabolism. Schick and Cohen[14] the same year studied convalescent children and reported that a low basal metabolic rate followed the exhaustion of fevers and infections and might last from one to several weeks. They believed that the low pulse characteristic of early convalescence was caused by the low metabolism.

Since higher basal metabolic rates are characteristic and normal for young children, all minus rates should receive careful attention as indicating a deviation toward an abnormal glandular condition. Inspection of the mean basal metabolic rates for this series indicates that any minus rate in a preadolescent child is below the accepted limits of normal, when the correction factor of minus 11.5 per cent is applied.

Examples are given in Table III where the basal rates when corrected with minus 11.5 per cent are all distinctly low.

TABLE III

PREADOLESCENT CHILDREN WITH SLIGHTLY MINUS BASAL RATES

CASE NO.	AGE	SEX	W-L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B. M. R. PER CENT	CALORIES PER HOUR
279	6	F	+3	+ 4.2	−3.6	34.5
258	7	M	−3	+ 4.4	−1.3	42.7
128	9	M	−3	+ 6.0	−2.8	44.3
115	8	F	+4	+ 4.3	−2.0	39.6
100	9	F	−5	+18.1	−4.1	41.2
101	4	M		+11.6	−1.5	36.1
102	8½	F	−4	+ 5.0	−1.5	39.2
153	7	F	+1	+ 4.2	−3.9	45.2
264	9	F	+1	+31.0	−4.0	49.5
295d	9	F		+17.0	−4.6	43.2
125a	8	F	+4	+17.7	−2.4	45.4
498	7	F	+7	+10.9	−4.2	43.0
427	5	F	+2	+ 1.0	−3.6	31.9

The Width-Length Index variation shows relative breadth, or percentage broader or narrower than average, for the age, sex, group.

Variation from average weight shows the percentage overweight referred to the Baldwin-Wood standard.

B.M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot standard.

Children below ten years of age with basal metabolic rates no lower than minus three or minus four (Benedict-Talbot standard) tend to put on weight readily and to be sluggish. These show marked improvement with a little thyroid therapy.

TABLE IV

LOW BASAL METABOLIC RATES IN BROAD-BUILT CHILDREN

CASE NO.	AGE	SEX	W-L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B. M. R. PER CENT	CALORIES PER HOUR
409	3	F	+10	+13.8	− 9.4	27.6
	4			+54.0	−23.3	30.9
	4			+27.0	−11.0	33.3
	5			+32.7	−21.8	30.6
349	6	M	+1	+12.6	−23.7	32.5
331	6	F	+1	+25.0	− 9.8	45.0
454a	6	F	+2	+24.5	− 6.5	40.2
318	7	M	+4	+18.6	−19.4	40.7
45	8	F	+4	+20.0	− 4.8	43.0
	8			+11.0	0.0	40.6
543	8	F		+28.0	− 7.1	46.6
154	9	M	−3	+28.7	−25.4	38.3
295b	10	M	+2	+28.8	−19.4	46.1
9	10	F	+5	+18.8	−18.5	42.2
450	12	F	+12	+25.2	−26.0	56.5
506	13	F		+48.1	−27.7	62.4
190	14	F	+13	+21.3	−19.6	56.5

The Width-Length Index variation shows relative breadth, or percentage broader or narrower than average, for the age, sex, group.

Variation from average weight shows the percentage overweight referred to the Baldwin-Wood standard.

B.M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot standard.

Twenty-eight of our cases in which the basal metabolic rate was very low were more overweight than the above group, and these children appeared with an entering complaint of obesity. Several of this group shown in Table IV were very broad-built with large width-length indices and all appeared to be markedly overweight. Their basal metabolic rates were low and became very low when corrected with minus 11.5 per cent. These children require thyroid treatment for a much longer period of time than the group in Table III, and need to stay on a restricted diet. They lose weight quite readily while taking thyroid, and most of them feel much better on thyroid than when not taking it. This group shows the extreme of the low variations and is close to the borderline of pathologic hypothyroid cases.

Very broad-built children often have low basal metabolic rates, and come in complaining of being overweight when they are not very much overweight for their build.

ANOMALOUS LOW BASAL RATES IN SLENDER UNDERWEIGHT CHILDREN

Dr. Hoskins[15] of the neuro endocrine research department at Harvard reported: "In addition to the sluggish, myxedematous type of deficiency as just described, there has come to be recognized in recent years

TABLE V

LOW BASAL METABOLIC RATES IN CERTAIN SLENDER-BUILT CHILDREN WHO ARE OFTEN ALLERGIC

CASE NO.	AGE	SEX	W-L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B. M. R. PER CENT	CALORIES PER HOUR
244	6	F	−7	−11.8	− 9.7	30.7
41	7	F	+1	− 5.0	− 7.6	38.9
553b	7	M,	−1	−11.2	−11.3	36.6
107	8	F	−2	− 8.8	−19.3	28.8
374	8	M	+2	−11.8	−13.8	38.5
215	8	M		− 7.3	−12.0	35.7
	9			− 2.1	− 9.5	42.5
562	9	M		−17.8	−11.3	38.3
394	10	M		− 6.2	−20.7	39.5
20	11	F		−12.8	−17.0	35.5
96	11	M		−14.0	−12.7	43.1
99	13	F	+5	− 3.5	−19.9	42.5
415	13	M	−7	− 7.8	−12.5	53.5
85	16	M	−2	−17.8	−17.0	43.7
532	18	F	+2	−10.6	−13.7	45.2
	18			−10.1	− 3.4	50.6

The Width-Length Index variation shows relative breadth of body, or percentage broader or narrower than average, for the age, sex group.

Variation from average weight shows the percentage overweight referred to the Baldwin-Wood standard.

B.M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot standard.

a thin, irritable nonmyxedematous type. The subjects, far from being phlegmatic, are overresponsive to environmental annoyances. The causal relationship of thyroid deficiency to the condition is indicated

by the marked diminution of the basal metabolic rate and is proved by increase of weight and restored placidity of disposition under thyroid medication."

Topper and Mulier[16] reported a group corresponding to one of ours that was underweight with low basal metabolic rates.

We have 67 cases showing moderately low basal metabolic rates in children, the majority of whom are slender-built and all of whom are under average weight referred to the Baldwin-Wood standards. These children might be expected to have high basal metabolic rates, both because of age and body build. Table V illustrates this group which deviates in the unexpected direction in basal metabolic rate. We have tried to find out what other things they share in common.

As a group they are fairly quiet youngsters with a heightened upper respiratory susceptibility. A large proportion of them (46 out of 67) are also allergic. (Their upper respiratory susceptibility may be on an allergic basis.) Upon examination, allergy was the most suggestive common denominator. Consequently, a direct analysis of our allergic children for whom basal rates were available, was undertaken to demonstrate, if possible, any existent metabolic trend.

BASAL RATES IN ALLERGIC CHILDREN

Out of a group of 72 allergic children, 58 had minus basal metabolic rates when corrected for age. The other 14 ranged from plus 12.1 per cent to plus 1.8 per cent. The average basal metabolic rate for the 72 was minus 5.8 per cent. The tendency of the group therefore was toward low basal metabolic rates.

Table VI shows the relationship between allergy and basal metabolic rate by age.

TABLE VI

THE BASAL METABOLIC RATE IN 72 ALLERGIC CHILDREN 26 OF WHOM HAD MULTIPLE MANIFESTATIONS

AGES	ASTHMA			ECZEMA			HAY FEVER			URTICARIA			GASTROINTESTINAL ALLERGY		
	NO. CASES	NO. B.M.R.	AVERAGE B.M.R.	NO. CASES	NO. B.M.R.	AVERAGE B.M.R.	NO. CASES	NO. B.M.R.	AVERAGE B.M.R.	NO. CASES	NO. B.M.R.	AVERAGE B.M.R.	NO. CASES	NO. B.M.R.	AVERAGE B.M.R.
0- 3	2	2	minus 17.2%	1	1	minus 19.9%									
4- 6	16	25	minus 4.9%	6	9	plus 5.3%	6	11	minus 8.1%	1		plus 27.2%			
7- 9	12	18	minus 9.8%	4	5	minus 1.6%	11	20	minus 5.7%	6	9	plus 4.0%	3	9	plus 11.1%
10-15	12	33	minus 4.8%	4	9	plus 1.3%	14	39	plus 0.6%	2	5	plus 1.0%	2	3	plus 3.6%
Total	42		minus 6.43%	15		minus 4.22%	31		minus 3.32%	9		plus 5.91%	5		plus 8.1%

Presented by age groups and showing averages compiled from 198 B.M.R. determinations on allergic cases.

Not all of our allergic children were slender-built with low basal metabolic rates. The babies with eczema were broader than average and for them metabolic studies are lacking.

Measurements to classify body build were done on 97 allergic children. The younger children had more eczema and the older ones more asthma and hay fever. See Table VII for the classification by age, sex, and build.

TABLE VII

BODY BUILD IN 97 ALLERGIC CHILDREN 23 OF WHOM HAD MULTIPLE MANIFESTATIONS

AGES	ASTHMA NO. CASES	ASTHMA AVERAGE BUILD	ECZEMA NO. CASES	ECZEMA AVERAGE BUILD	HAY FEVER NO. CASES	HAY FEVER AVERAGE BUILD	URTICARIA NO. CASES	URTICARIA AVERAGE BUILD	GASTROINTESTINAL ALLERGY NO. CASES	GASTROINTESTINAL ALLERGY AVERAGE BUILD
		3.0%		0.6%		1.0%		0.2%		1.6%
0- 3	4	Narrow	9	Broad	2	Narrow	5	Broad	3	Broad
		3.5%		1.3%		Exactly		2.0%		2.0%
4- 6	18	Narrow	7	Broad	7	Average	1	Broad	1	Broad
		2.0%		0.5%		3.1%		3.7%		5.0%
7- 9	11	Narrow	2	Broad	8	Narrow	4	Narrow	5	Narrow
		4.4%		0.7%		3.6%		11.0%		0.7%
10-15	16	Narrow	3	Narrow	14	Narrow	1	Narrow	3	Broad
		3.4%		0.5%		2.4%		2.1%		1.3%
Total	49	Narrow	21	Broad	31	Narrow	11	Narrow	12	Narrow

Presented by age groups and showing average body build in terms of percentage broader or narrower than the mean for age and sex.

The total allergic group averages 2.16 per cent narrow.

Body measurements to distinguish build were recorded in terms of percentage broader or narrower than average for age and sex. The children with asthma and hay fever were consistently slender-built with minus basal metabolic rates. Those with eczema were slightly broader than average and had variable basal rates. The children with urticaria and gastrointestinal allergy showed no consistent type of body build and their basal rates as a group ranged above average.

Whether there is a causal relationship between low basal metabolic rates and certain allergic tendencies in children is a question that merits further study. At the present time we can say only that in our group of slender-built children with basal metabolic rates lower than average for their ages, and lower than average for their build, 68 per cent were allergic. In addition to this, 80 per cent of our allergic children, who had basal metabolic rate determinations done, had minus rates. Perhaps the constitutional factor in allergy is similar to the constitutional factor which causes the unexpected direction of variation in the basal metabolic rates.

Constitutional influences on basal metabolism are reported by the White House Conference to be:

1. Those hereditary factors which affect body size and proportion.
2. Those which affect nervous organization.

3. Those which produce a tendency to leanness or fatness, aside from the endocrine functions.

4. The endocrine factors themselves.

The report further points out that there are great varieties of body shape and size which possess normal endocrine functions and that

1. The presence of bone diminishes the metabolism per unit of mass while the presence of large amount of muscle increases it.

2. A highly nervous or hysterical temperament accentuates the basal rate while a phlegmatic temperament lowers it.

We have previously pointed out that broad-built children have larger bony frameworks than slender-built ones who have better muscles. Our personality and heredity studies have shown that, in general, our slender-built children are much more nervous, high-strung, and easily fatigued than our broad-built children, who are, in general, slower and more easy-going. All of these things are corroborative of the findings of the White House Conference Committee since our slender-built children consistently had higher basal rates than our broad-built ones, even though we had one group of slender children with low basal rates which were averaged with the other slender-built children.

CONCLUSIONS

1. A group study of any biologic data helps to establish trends in the general population and to diagnose normal variations for the individual.

2. The individual case cannot illustrate all the elements that make up the group classification, nor can one case meet all the requirements that result in the conclusions drawn from a group study.

3. Such a group study of 1,334 basal metabolic rates in 680 children shows every gradation from high to low rates.

4. The basal metabolic rate decreases regularly from early childhood to adolescence, where it reaches the adult level.

5. Other physiologic data, such as pulse rate and body temperature, parallel the basal metabolic rate in its age level variations, tending to emphasize the reasonableness of the finding.

6. High basal metabolic rates are characteristic of slender-built children regardless of age, and low rates are characteristic of broad-built ones.

7. Since the higher basal metabolic rates are characteristic and normal for young children, all minus rates should receive careful attention as indicating a deviation toward an abnormal glandular condition.

8. Children under ten years of age with slightly minus basal metabolic rates tend to put on weight readily and to be sluggish.

9. In our group of slender-built children with basal metabolic rates lower than average for their ages, and lower than average for their build, 68 per cent were allergic. In addition to this, 80 per cent of our allergic children, for whom there were basal metabolic determinations, had minus rates.

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MULTIPLE CONGENITAL RIB AND SPINAL DEFORMITIES

Report of a Case

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COMPARATIVELY little was known of rib and spinal anomalies prior to the development of roentgenology as a science and the widespread use of the x-ray in the diagnosis of bone conditions. It has become increasingly more evident that particular examples of congenital malformations of the skeleton are usually associated with other bone defects. For example, cases of absence of ribs are invariably associated with corresponding vertebral malformations.[1]

Various congenital anomalies may occur in rib formation. Among these anomalies may be mentioned:

Cervical ribs
Variations in size and shape
Bifurcation
Fusion
Total absence of one or more ribs
Lumbar ribs

Cervical ribs have been known for centuries. Galen (A.D. 200) mentions cervical ribs. Much has been written on this subject in recent years as many of the cases mentioned were discovered accidentally by x-ray.

White[2] states that of 5,728 chests examined with x-rays for various conditions other than anomalies, about 1 per cent showed congenital variations of all types. He states further that 20 cases of this series showed cervical ribs.

Henderson[3] records 31 cases of cervical ribs in the routine examinations of approximately 80,000 patients. Eighteen of the 31 gave no subjective symptoms. Eleven of the 18 did not show a tumor and all had been subjected to an x-ray examination of the chest for some other reason: question of tuberculosis, for large heart, for determination of possible substernal goiter, for possible aneurysm.

Cushway and Maier[4] found 3 men with cervical ribs of 931 applicants whose spines were filmed routinely as a check-up for any possible abnormality before they were permitted to work as switchmen.

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Because lumbar ribs are seldom of any clinical significance, the literature makes little of this anomaly. That they occur more often than is suspected can be deduced from the fact that Cushway and Maier report, in their series, 81 patients with ribs attached to the first lumbar vertebra as compared to 3 in whom the ribs were attached to the seventh cervical vertebra.

Giles[5] made 8,000 spine examinations and found 1,122 showing anomalies. Seventy-three of these 1,122 disclosed lumbar ribs.

Cumming[6] reports a case of a rib arising from the transverse process of the third lumbar vertebra. The rib curved downward and fused with the transverse process of the fourth lumbar vertebra of the same side. This rib was discovered after an examination for pain in the back. The rib was fractured as the result of injury.

As to the variations in the sizes and shapes of ribs, White[2] found considerable variations in the size of the first rib. Sometimes the first rib was almost as thin as a cervical rib. In other cases it was broad and failed to articulate with the sternum although the corresponding cartilage was completely calcified.

Hrdlicka[7] says that he found the third rib, particularly its sternal half, more subject to modification; and the eleventh and twelfth differing much more in size than in shape.

Absent ribs have been reported by a number of observers. Steindler[1] gives a short résumé of the literature on this condition and says, ". . . . a distinction should be made between the partial defects of ribs and sternum which are comparatively common, and the total defects of one or more ribs which are extremely rare."

Sever[8] examined several thousand films which had been taken of patients in the orthopedic department of the Children's Hospital in Boston and discovered a number of cases of absent ribs.

There are not many examples of true bifurcation. Among these may be mentioned one by Bloomberg[9] who cites a case of a boy, four years old, who had bifurcations of the third and fourth ribs on the right side.

Dennis[10] cites 3 cases: 2 of the fourth right rib and 1 of the third left.

Ruppricht[11] discusses the case of a fetus in which he found bifurcations of the third and fourth ribs both on the right side.

Hrdlicka[7] found 6 specimens of forking, of which only one specimen was on the left side. The sternal extremity was the part affected.

Struthers[12] describes 5 specimens and Adami[13] 3. These were all at the sternal extremity, mostly limited to the cartilage, and not very great in extent.

Fused thoracic ribs are among the uncommon anomalies. Hrdlicka[7] examined 1,000 first ribs, 1,200 second ribs, and 14,000 ribs other than first and second. Of this large series, there were 4 specimens of fusion. He found 2 additional examples among ribs of American Indians. This anomaly was on the left side in 5 out of the 6. In 2 of the 6, there was a junction of a cervical with the first rib; in 3, a junction of the first and second; and in 1, a junction of the third with the fourth rib. In both cases of the union of the cervical rib with the first, and in one case of union of first with the second, the superior rib descended to fuse with the inferior one. The sternal part of these 3 specimens

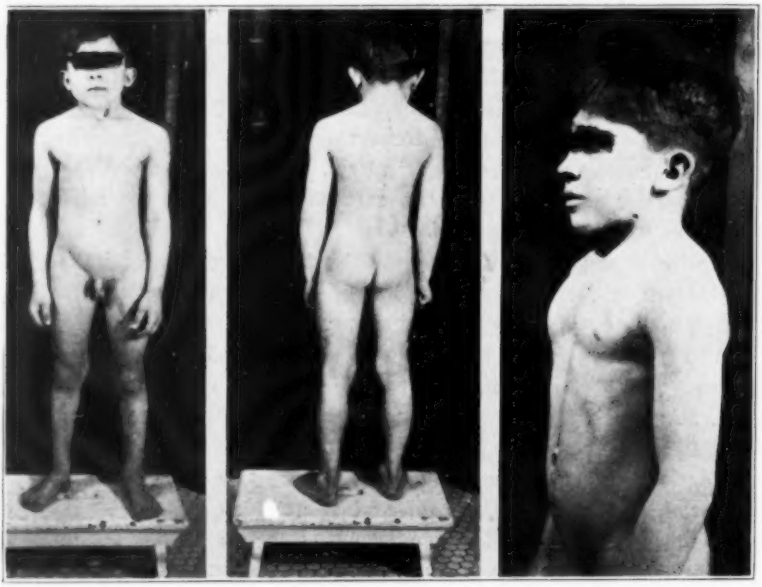

Fig. 1.—Photograph taken May, 1933. Front view showing head inclined to the right and right shoulder higher than the left.
Fig. 2.—Photograph of back taken May, 1933, showing dorsal scoliosis.
Fig. 3.—Side view. Note bulging of right chest wall anteriorly.

showed no abnormality. In the remaining 3 specimens, the anomaly consisted "in an extension and more or less extended fusion of the neighboring borders of the ribs. In these cases we have seemingly a combination of a bicipital and bicaudal rib."

Meyer[14] presents a specimen showing fusion of the second and third ribs of the right side throughout three-quarters of their length. He mentions other cases cited in the literature from which one may infer that the anomaly occurs most often between a cervical and a first, and less often between the ribs next in order of their sequence, becoming extremely rare below the fourth rib. Indeed, Meyer tells

of only one case of fusion below the fourth rib and that, supposedly in a seven-month-old fetus which was said to have been in the possession of Hunauld.

Ruppricht[15] describes a fetus with union between the first and second ribs on the left side. He found 57 cases of rudimentary first ribs in the literature from 1820 to 1926. In 21 of the 57 cases, there was some kind of union to the neighboring rib. The union was bony, cartilaginous, or otherwise. He found a higher ratio of union when cervical ribs were present. In only 12 of all cases found was there a continuation with the sternum. Where the first rib was beyond the rudimentary stage, he found 7 cases of union between the first and

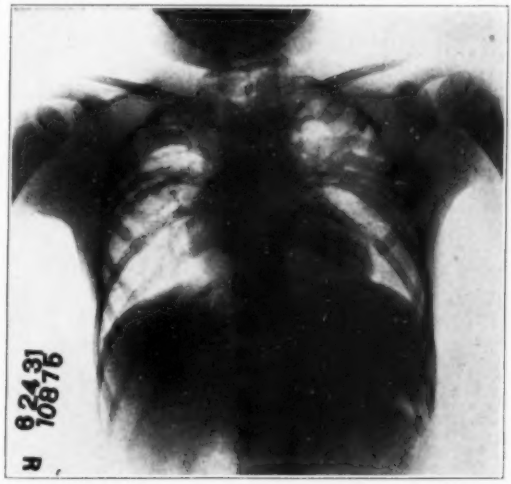

Fig. 4.—Roentgenogram of chest. There is a fusion of five ribs into a sort of bony plate in the middorsal region of the left side.
On the right side, there is a union of two, three, or more ribs in the upper dorsal region and another union of two ribs below this.

second ribs. In cases with fully developed ribs, he found 3 instances cited; and he himself chanced upon 2 other specimens in the Vienna Institute of Pathology.

Rees[16] examined a six-year-old girl who had a congenital scoliosis and found, among a number of bony defects, a union between the second and third ribs on the right side.

Gurney[17] reported the case of a six-year-old girl who had what he describes, "..... ribs, many of them amalgamated at the back, two, and in one case three, springing from the spine as one bone which separates into two (or three) about two inches from the middle line."

Hatch and Plume[18] report a case of a seven-year-old girl in whom

they found the sixth and seventh ribs fused for a short distance beyond their tubercles where the mass divided into four ribs varying in size.

Sever[8] presents a number of children with very gross deformities, among which I could make out 8 to 10 well-defined cases of fusion below the fourth rib. In 1 case there was fusion between the ninth and tenth ribs, and in at least 4 cases there was a fusion of three or more ribs. In Sever's cases the anomaly was about equally divided between the right and left sides.

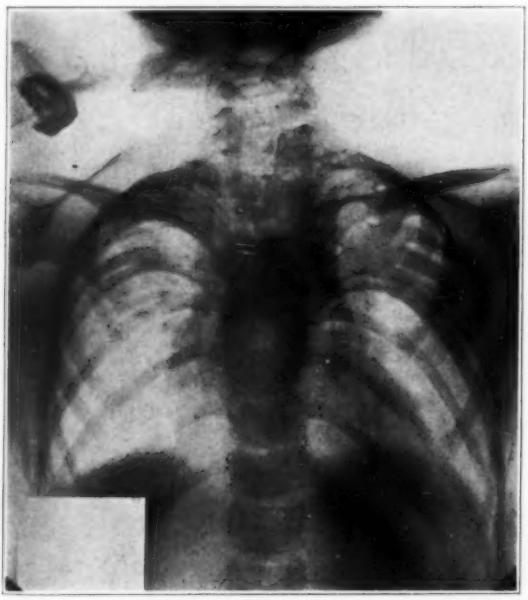

Fig. 5.—Roentgenogram of the spine in the cervicodorsal region. Note the extensive spina bifida occulta and disorganization of the vertebral bodies.

SPINAL ANOMALIES

Spinal anomalies have been reviewed, in recent years, by a number of authors. Danforth,[19] in an interesting paper on numerical variations in vertebrae, contends that the vertebra is in a sense plastic and this character of the vertebra is largely a function of its position. To this may be added Cushway and Maier's statement that examination of the individual vertebrae in their series revealed an approximation to the so-called average vertebra though none were found identical. "Each spine is characteristic of the individual, and he may be identified by a roentgenogram of the spine just as definitely as by a photograph of the face or by finger prints."[4]

Willis,[20] in a very interesting article, concludes as follows:

"1. The number of cervical vertebrae had been found practically constant not only in man but throughout the mammalian class.

"2. The number of coccygeal segments is of negligible importance.

"3. The vertebrae may be divided into two main groups, presacral and sacral.

"4. Variation in the number of lumbar vertebrae is often coincident with, and compensated by, a reverse variation in the thoracic group. Likewise, at times, coincident with the lumbar variation a

Fig. 6.—Roentgenogram of the lumbosacral region. There are six lumbar vertebrae. The sacrum is curved with convexity to the right. The first sacral segment shows a spina bifida occulta, a transverse process of the lumbar type on the right, and a lateral mass on the left.

reverse variation occurs in the number of sacral segments." With this in mind, and also basing his opinion on the studies made by Todd[21] on the comparative evolution of the vertebral column in the mammalia, he found a presacral numerical stability of 95.8 per cent.

Bohart[22] says, "Anomalies of the spine exist from statistics available in from 8 to 10 per cent of all persons examined." This, of course, includes all types of anomalies, both congenital and acquired.

A consideration of congenital anomalies of the spine entails a long list of malformations. For our present discussion, it will be necessary

to give only a very brief outline of the more obscure conditions. Among these we may consider:

Spina bifida occulta
Variations in the body of the vertebra
Defect in the lamina
Congenital anomalies of the cervical spine
Numerical variations in the thoracolumbar region
Sacralization
Low lumbar, sacral, and coccygeal deformities

Spina bifida occulta is, by far, the most common congenital anomaly found in the spine. It may be found in any position of the vertebral column but more especially in the lower lumbar and sacral regions, the latter position being the most frequent site. Clinical manifestations do not necessarily accompany this deformity.

Variation in the formation of the vertebral body itself, is not common. The deformity may consist in a hemivertebra or otherwise malformed or displaced vertebra. When found in the thoracic region, one may expect some defect or abnormality in rib formation. Thus, in the cases cited by Sever and Rees, the thoracic spine showed this abnormality.

Incomplete union of the lamina is another deformity which is not common. Willis found 4.28 per cent of skeletons with this deformity. Cushway and Maier found only 2 cases in their series of roentgenograms in which the lamina was not united with the transverse process.

Congenital anomalies of the cervical spine are uncommon. Especially rare are those described under the obscure term of Klippel-Feil syndrome. This consists in a numerical variation in the cervical vertebrae with more or less complete fusion into one mass, accompanied, in some cases, with spina bifida or other anomalies.[23]

Meisenbach[24] reports a case of total absence of the cervical spine in a girl ten years old.

Reference has already been made to numerical variations in the thoracic and lumbar regions. This anomaly is much more frequent in the lumbar region than it is in the thoracic region; but as Giles[5] puts it, an absent twelfth rib may give one the impression that he is dealing with six lumbar vertebrae when the reverse may be the case. Giles found 50 cases with six lumbar vertebrae and 13 with four lumbar vertebrae. Cushway and Maier found 25 cases with six lumbar vertebrae, 6 with four lumbar vertebrae, and 5 with thirteen thoracic vertebrae. Each of the last 5 had thirteen ribs.

Sacralization, or articulation between the transverse process of the fifth lumbar vertebra and the sacrum, is the most common congenital anomaly of the spine next to spina bifida occulta. There seems to be a great divergence of opinion as to the importance of this condition

and as to what does and what does not constitute true sacralization. It will be sufficient for our purpose to say that there are many different degrees of sacral transformation of the fifth lumbar vertebra; and that actual contact of bone, per se, may not give rise to symptoms. The bilateral occurrence is more frequent than the unilateral.

Coccygeal deformities are not painstakingly analyzed because most of them are of minor clinical significance and are usually considered along with sacral or other pelvic deformities.

Anomalies of the fifth lumbar are common, and anomalies of the low lumbar and sacrum are most common.

There may be what is sometimes termed "asacralization" or "lumbarization," in which the uppermost part of the sacrum takes on the characteristics of a lumbar vertebra.

Lastly, there may be variation in the number of sacral segments or separation between them, and accompanied by other associated malformations.

CASE REPORT

A white boy, five and a half years old, was brought to the clinic of the New York Nursery and Child's Hospital on June 24, 1931, because he was stunted in growth. The only previous history in connection with the deformity was an asymmetry in the chest wall which was first noticed when the child was two and a half years old.

The father and mother were both in their twenties and well. There was one other child, a boy aged seven years, who was apparently of normal physical development. The remainder of the family history was essentially negative.

Examination disclosed a boy 37 inches in height and weighing 29½ pounds. He did not appear to be very strong and talked in a weak, almost piping voice. He had much dental caries. His head was inclined to the right. There were two small papillomas anterior to the tragus of his right ear. The crus antihelicis and the antihelix of this ear were sharply ridged. The right shoulder was higher than the left and a scoliosis was present. There was a bulging about the size of a plum in the midportion of the right chest wall anteriorly. There was a systolic murmur heard at the apex and at the pulmonic area, but more pronounced at the latter.

A roentgenogram of the chest disclosed the uppermost ribs so closely grouped on both sides that it was difficult to distinguish their individual outlines. Somewhat below this, on the left side, there was fusion of at least five ribs into a sort of bony plate. On the right side, there was one union of two, three, or more ribs and another of two ribs directly below this. The ribs on this side did not seem to be in contact with the spine. The lowest four ribs on the left and the lowest three on the right appeared to be normal. The dorsal vertebrae, with the exception of the last three which were apparently normal, were of irregular shape and size and showed spina bifida occulta. There was also a scoliosis in this region with convexity to the right. The lumbar spine showed six vertebrae. The first sacral segment was asymmetrically developed and showed a lateral mass on the left side articulating with the ilium, and a transverse process of the lumbar type on the right. There was marked pelvic asymmetry with deviation of the distal, sacral segments to the left. There was a spina bifida occulta of the first sacral segment. The innominate bones were normal.

No abnormalities were found in the roentgenograms of the skull or long bones.

A few months after the first visit, the patient left for the country, and we did not hear from him until January, 1933.

On Jan. 23, 1933, his height was 41¼ inches and his weight 33¾ pounds. A Mantoux test with 0.02 milligrams of tuberculin resulted in a very strongly positive reaction. The mother later informed me that the child had frequently been in the company of a man who had since died of pulmonary tuberculosis. No definite signs could be found in his chest and he was referred to the x-ray department. A roentgenogram of the lung fields was taken on Mar. 15, 1933.

The roentgenologist reported that the left hilum shadow appeared to be more dense and of nodular form. This was diagnosed as adenopathy of the left hilum.

The child is now in school and the report from the teacher states that he is studious, his work is satisfactory, he is always neat and clean, and socially very amiable. He is well liked by the other children in the class.

SUMMARY AND CONCLUSIONS

An outline of some of the more obscure congenital abnormalities of the ribs and spine is presented. To this is added the report of a boy having unusual deformities of this character.

The abnormalities discussed here can be correctly diagnosed only by x-ray or postmortem examination.

Cervical ribs, although not uncommon, are not as frequent as lumbar ribs.

Total absence, bifurcation, and fusion may be listed among the rare congenital rib conditions.

Spina bifida occulta is the most common finding and sacralization is next to it in frequency.

Numerical variations in the thoracolumbar region are not rare. Six lumbar vertebrae are found more often than four and both of these variations are more usual than thoracic variations.

Variations in the body of the vertebra and defect in the lamina itself, are found less frequently.

Absence of cervical vertebrae is rare. Reference is made to a case of total absence of the cervical spine.

The most common site for congenital spinal abnormalities is the lumbosacral region.

A report is given of a boy having a congenital scoliosis and showing a peculiar type of fusion of ribs. There are also extensive spina bifida occulta, irregularities in the vertebral bodies, and widespread sacral malformations.

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2349 TWENTY-SIXTH STREET

VITAMIN D DEFICIENCY

Tetany in Infants Without Rickets

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FIVE infants with tetany, unassociated with roentgenologic evidence of rickets, are reported. That the tetany was dependent on a deficiency of ultraviolet radiant energy or vitamin D is evidenced by the prompt response to antirachitic therapy.

The essential data are summarized in the table and the roentgenologic findings are illustrated in Fig. 1. All infants received cow's milk in various dilutions during the hospital stay. One (Case 2) received 2 grams of calcium chloride during the first day of treatment. No calcium was given to any of the others.

Fig. 1.—Roentgenograms of five infants with tetany unassociated with rickets.

In all 5 infants treatment with antirachitic agents resulted in a prompt and complete disappearance of symptoms and a return of the serum calcium and the electrical reactions to normal.

A number of other infants have been observed with tetany but without roentgenologic evidence of rickets (24 out of 125 cases). They are not presented here because they either left the hospital before cure was complete, or the results of specific treatment were obscured by the administration of calcium in fairly large amounts.

That a deficiency of sunlight or vitamin D may be present without rickets is suggested by the studies of Daniels[1] who found a striking improvement in the calcium and phosphorus retentions in seemingly normal infants following the addition of cod liver oil to the diet or the irradiation of the milk in the feeding. Swanson[2] noted a similar improvement in the phosphorus and calcium retentions in 2 infants with-

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TABLE I

THERAPEUTIC RESULTS WITH ANTIRACHITIC AGENTS IN FIVE INFANTS WITH TETANY AND WITHOUT RICKETS

CASE NUMBER	AGE MONTHS	SYMPTOMS	ANTIRACHITIC TREATMENT	BEFORE TREATMENT		AFTER TREATMENT		DURATION OF TREATMENT (DAYS)
				SERUM CALC. (MG. PER CENT)	SERUM PHOS. (MG. PER CENT)	SERUM CALC. (MG. PER CENT)	SERUM PHOS. (MG. PER CENT)	
1	6	Convulsions, laryngospasm active facial C. O. C. = 2.0*	Vigantol† Cod liver oil	6.5	4.3	10.2	5.7	7
2	1¾	Convulsions C. O. C. = 4.0*	Viosterol‡	7.0	9.4	9.4	7.4	12
3	16	Laryngospasm	Cod liver oil	7.7	5.6	9.9	—	5
4	5	Convulsions, positive peroneal C. O. C. = 4.8*	Ultraviolet radiant energy	6.8	7.1	11.1	6.1	7
5	5	Active facial, nystagmus, laryngospasm	Vigantol†	6.7	8.2	10.6	6.3	18

*C. O. C. Cathodal opening contraction in milliamperes.
†Vigantol is an unstandardized proprietary preparation of irradiated ergosterol of high antirachitic potency.
‡Received 2 grams of calcium chloride during first day in hospital.

out roentgenologic evidence of rickets and with normal values for the serum calcium and phosphorus, following the addition of cod liver oil to the diet.

SUMMARY

1. Tetany in infants may occur without roentgenologic evidence of rickets.

2. That this form of tetany is dependent on sunlight or vitamin D deficiency is evidenced by the prompt response to antirachitic therapy.

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ADVANTAGES OF STRAINED SOLIDS IN THE EARLY MONTHS OF INFANCY

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DIFFERENCE of opinion still exists as to the best age at which to begin to feed cereals, egg yolk, strained fruits, and strained vegetables to a well baby. Morse,[1] who represents the most conservative group, expressed the belief that cereal may be fed at the age of nine months, and advised a full diet at the age of one and a half to two years. Hess[2] and Brennemann,[3] on the other hand, say that from five to eight months is the proper age for a full diet. Brennemann[4] believes that introduction of solids into the infant's diet in comparatively early infancy (fifth and sixth months) is advantageous, because the solids (1) contain vitamins, (2) have value in infant psychology, (3) are easily tolerated, and (4) contain iron which is necessary. The earlier introduction of solids is not only advocated by most physicians but is practiced by most mothers.

The object of my study was to determine the best age at which to introduce solids into the well baby's diet, and to observe whatever advantages or disadvantages were presented by the early introduction of solids.

METHOD OF STUDY

A study was made of 231 infants who were observed in the Well Baby Clinic[5] in the Roslindale District of the city of Boston in the years 1930 and 1931, and the first six months of 1932. This district contained, for the most part, people of good social and hygienic surroundings, in moderate economic circumstances. The infants received medical care, supported by nursing care from a group of well-trained nurses connected with the clinic.

Solids were fed in the early months of infancy in such a way as to supplement the milk (breast or bottle) the infant got, but not to complicate the feeding routine. This was done because too often mothers feed the infant as if he were a machine. For example, the mother gives an infant one teaspoonful of carrots, two teaspoonfuls of spinach, and seven ounces of milk. In this way she pays no attention to the natural power of selection of the infant, although the appetite of an infant will vary from day to day and from meal to meal. I believe that an infant should be allowed some choice as to the amount and kind of food which he receives. This has scientific support, for in 1915, Ewvard[6] allowed a group of hogs to select whatever they wished and as much as they wished from an assorted variety of basic foodstuffs. The amount and type of food actually eaten by the hogs was found best for their nutrition and development. Cowgill,[7] in 1928, showed that dogs also are able

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to choose for themselves the optimum amounts of a complete food. Davis,[8, 9] in 1927 and in 1928, showed that this power of selection was correct in newly weaned normal, anemic, and rachitic infants.

This natural power of selection of food by the infant was utilized in this study. At all times the infant was allowed to take as much food as it wished. Bottle-fed infants were prescribed formulas containing milk, water, and sugar (Mead's dextri-maltose, Karo syrup, milk sugar, or cane sugar). Three teaspoonfuls of cod liver oil and three ounces of orange juice daily were prescribed (summer or winter) for every infant. Cod liver oil, however, was omitted during a hot spell or whenever the infant's appetite was impaired. The infants were seen once a week or once in two weeks, and the formula was changed as the indication arose.

When solids, such as fine wheat or barley cereal, were introduced into the infant's diet, the mother was instructed to teach the infant to swallow them. Ordinarily an infant from two to four months old easily learned to swallow the well-cooked and strained cereal that was softened with milk. Occasionally, it took two weeks (twenty-eight attempts) to teach a determined infant six to eight months of age to swallow solids. When the infant learned to take cereal, the mother was told to give it all it wished. As more cereal was taken, less sugar was included in the formula. The cereal was given at 10 A.M. and 6 P.M. and was followed by bottle or breast. After the infant learned to take cereal well, Zweibach, toast, egg yolk (cooked ten minutes), strained fruits, and strained vegetables were added to the diet. One teaspoonful of a new food was tried at one feeding and old foods could be mixed if desired. After the solids were eaten, the infant was allowed to take as much milk as it wanted. The following rules were emphasized: (1) boil everything the infant eats; (2) start only one new food a day, one teaspoonful at first, gradually increasing the amount; (3) give solids at the beginning of the feeding; (4) let the infant eat as much as it wants; (5) never force the infant to eat, and (6) if the infant refuses food, give water and orange juice until the next feeding time, and repeat this procedure until it is hungry.

The full diet of solids was as follows: (1) at 6 A.M., milk (formula, whole milk, or breast milk); (2) at 8 A.M., cod liver oil and orange juice; (3) at 10 A.M., cereal or Zweibach, and milk; (4) at 2 P.M., (a) broth or beef juice, (b) egg yolk, (c) potato, rice, or macaroni, (d) strained green vegetable (two of the following: spinach, peas, string beans, stewed celery, carrots, squash, stewed tomatoes), and (e) milk; (5) at 6 P.M., (a) cereal or Zweibach, (b) apple sauce, prune pulp, or strained apricots, and (c) milk; (6) at 10 P.M., milk if the infant is awake. During the eighth, ninth, and tenth months, simple desserts, such as Jello, junket, and sherbet, prepared cereals, and strained meats were added to the diet.

RESULTS

The 231 infants that were fed in the manner described were divided into four groups according to the age at which solids were first given: Group I, during the second and third months, 38 infants; Group II,

TABLE I

WEIGHT IN RELATION TO SITTING HEIGHT

	NUMBER OF INFANTS	PER CENT WITH WEIGHT WITHIN THE CALCULATED NORMAL WEIGHT RANGE BASED ON SITTING HEIGHT
Group I	15	87
Group II	11	82

during the fourth month, 53 infants; Group III, during the fifth and sixth months, 97 infants, and Group IV, during the seventh, eighth, ninth, and tenth months, 43 infants. Each group was studied for (1) nutrition and development, (2) effect on the gastrointestinal tract, and (3) effect on food habits.

TABLE II

WEIGHT (IN POUNDS) ACCORDING TO AGE

	BIRTH	2 MO.	4 MO.	6 MO.	8 MO.	10 MO.	1 YR.
Group I	7.7	10.6	14.5	17.5	20.0	21.7	23.3
Group II	7.5	10.3	14.0	16.8	19.2	21.1	22.7
Group III	7.5	10.3	13.5	16.3	19.1	20.6	22.0
Group IV	7.7	10.7	14.0	16.6	18.7	20.5	22.4

Nutrition and Development.—Weight was regarded not only as a measure of the infant's nutrition, but also in relation to the skeletal structure. For a number of infants observed in Groups I and II, it was possible to record the so-called normal weight as calculated from the sitting height of the infant,[10] and to compare this normal weight with the actual weight of the infant. Thus, if certain groups show an unusual

TABLE III

DEVELOPMENT

	NUMBER OF INFANTS	DENTITION, MONTHS	TIME OF WALKING, MONTHS
Group I	32	6.5	12.1
Group II	31	6.6	12.5
Group III	70	7.2	12.8
Group IV	27	7.5	13.4

gain in weight, this gain in weight is desirable when it approximates the normal weight as calculated from the sitting height.

Thirteen of the 15 infants in Group I, and 9 of the 11 infants in Group II, whose calculated normal weights were recorded, had actual weights within calculated normal limits (10 per cent), as shown in Table I.

In Groups I and II (solids given early), the yearly average gain in weight was respectively 0.9 and 0.7 pound greater than the weight gained in a year by infants of corresponding birth weight in Groups III and IV (solids given later). The weight of each group is given in Table II.

Dentition occurred earlier in the groups in which solids were introduced into the diet early, as shown in Table III. Furthermore, the age at dentition in Group I was one whole month earlier than in Group IV.

There was also a definite relationship between early walking and early feeding of solids, as shown in Table III. The infants in Group I started to walk at an average of 12.1 months, while the infants in Group IV started to walk at an average of 13.4 months.

Effect on the Gastrointestinal Tract.—The solids were easily digested in all the groups, which included 166 infants. In the groups in which solids were given early there were fewer gastrointestinal disturbances associated with extraintestinal causes, and far fewer disturbances directly related to the gastrointestinal tract.

The first time strained vegetables were given, whether early or late, most of them were observed in the stool without much digestion, and they colored the stool. Carrots, beets, tomatoes, and string beans were well digested the second or third time they were eaten. Spinach required four to five attempts before it was digested to any appreciable degree.

TABLE IV

EFFECT ON THE GASTROINTESTINAL TRACT

	NUMBER OF INFANTS	PRESENCE OF CONSTIPATION		PRESENCE OF GASTRIC DISTURBANCES	GASTRIC DISTURBANCES WITHOUT EXTRA-INTESTINAL CAUSES
		BEFORE DIET ADDED	AFTER DIET ADDED		
Group I	28	38.6%	11.5%	28.5%	3.5%
Group II	37	37.9%	10.8%	29.7%	5.4%
Group III	73	41.1%	12.3%	45.7%	18.5%
Group IV	28	53.5%	32.1%	32.1%	17.9%

TABLE V

EFFECT ON FOOD HABITS

	NUMBER OF INFANTS	PRESENCE OF FAULTY HABITS	ENJOYMENT OF FOOD	PRESENCE OF FOOD DISLIKES
Group I	26	69.2%	93.0%	42.7%
Group II	37	43.3%	89.2%	35.1%
Group III	71	52.1%	77.0%	50.7%
Group IV	27	63.0%	77.7%	51.8%

In a few cases in which a wide variety of new cereals, vegetables, and fruits were tried within a few days an interesting syndrome developed. The infant took the foods well, was active, slept well, and had a bowel movement once or twice a day, which was brownish or the same color as the vegetables. There was no gain in weight and sometimes even a loss of one to two ounces for a week, but after this the gain was within normal limits.

When cereal was added to the diet, the character of the stool changed very little. In some cases the stool became softer and occurred twice a day instead of once. The addition of egg yolk to the diet gave the stool a golden brown color. In a few cases vomiting occurred, but this was due to egg-idiosynerasy. When a bowel movement is soft, semisolid, ranging in color from yellow to brown, having very little odor, and occurring regularly once or twice a day, it is safe, as a rule, to say that the type of food ingested is proper.

The groups in which vegetables were given early showed a definite decrease in chronic constipation (Table IV). Constipation was present in about 40 per cent of the cases, but the earlier a diet containing solids was given the fewer the cases of chronic constipation. Although 70 per cent of the constipated infants of less than seven months of age were relieved by the addition of solids, only 40 per cent of the infants from seven to ten months of age were so relieved.

Effect on Food Habits.—Each group was studied as follows: (1) presence of faulty habits, such as temper tantrums, crying to be picked up, wishing own way, and difficulty in sleeping, (2) enjoyment of food, and (3) definite dislike of any food or foods.

The results (Table V) show that the groups fed solids early had better food habits and fewer food dislikes than those fed solids later. Group I had 7 per cent more food dislikes than Group II, but in the presence of 26 per cent more faulty habits in Group I the result was not so striking, since there is a tendency for food dislikes among infants with faulty habits.

Explanation of Results.—A sufficient amount of vitamins and minerals is necessary for proper nutrition and development of an infant. Frequently breast milk or formula milk does not fully supply this need, even with the addition of average amounts of cod liver oil and orange juice. Apparently the reason why a full diet of solids is desirable is not that breast or bottle food does not contain the vitamins but rather that they are often contained in insufficient quantity.

A full diet of strained solid foods supplies an abundance of vitamins A, B, C, and D. Such a diet gives an oversupply of vitamin A, which may be stored in the body, and used when needed, thus increasing vigor and resistance to disease.[11] Vitamin B is often deficient in either human or cow's milk.[12, 13, 14, 15, 16] The amount of vitamin C necessary to prevent scurvy is only a fraction of the optimum amount needed. Vitamin D is particularly required in the metabolism of phosphorus and calcium.[17] Wilson[18] made roentgenographic examination of infants who had received cod liver oil and found rachitic changes in the bones of 97 per cent of those examined, probably due to an inadequate amount of cod liver oil, for Hess[19] believes that at least 15 c.c. of cod liver oil daily are necessary to supply the vitamin D content necessary to prevent rachitic changes in the average infant. The diet of strained vegetables possesses all of these vitamins in adequate quantities to effect proper development and nutrition for a normal infant.

Although cow's milk and human milk contain all of the minerals necessary for development, both are conspicuously deficient in iron. Rapid growth and increased production of blood in the newborn infant[20]

depend upon a reserve of iron deposited in the liver. The liver of the newborn animal contains at least five times as much iron as is found in the liver of the full-grown animal.

Since milk is deficient in iron, one might expect the hemoglobin content of blood to be much higher at birth than in later infancy. Williamson,[21] in 1916, proved this to be true. He showed that newborn infants average 23.2 gm. of hemoglobin per 100 c.c. of blood, that by the end of the second month the hemoglobin drops to 18.3 gm., that by the end of the fifth month it drops to 13.7 gm., and that the drop continues until at the end of the twelfth month the hemoglobin is 12.5 gm. per 100 c.c. of blood.

The German investigators, Schwartz, Baer, and Weiser,[22] could not find, by histologic examination, any iron in the infant's liver or spleen after the fifth month. This means that all the iron stored in the newborn infant's liver is completely used up before the sixth month, and thereafter the infant is entirely dependent for iron on the intake of food. Mayers[23] suggested that the drop in hemoglobin during the first year of the infant's life is a nutritional anemia, resulting from faulty feeding.

The amount of iron required daily by an infant has not been determined. Morse[24] has expressed the belief that 0.5 mg. of iron daily is sufficient for the first six months, and that 1.5 mg. of iron daily is necessary for the second six months. Larger amounts of iron, however, could well be used, for there is a definite relationship, within certain limits, between intake of iron and increase in hemoglobin. The addition of strained solid foods in the early months of infancy supplies a diet rich in iron and helps to prevent the nutritional anemia frequently present.

The infants in my series showed definite ability to digest strained solids, even in the early months of infancy (second and third months). This easy digestibility may be due to the recent great improvement in the manufacture of strained fruits and vegetables. Caldwell,[25] in his series of 60 infants, showed that strained vegetables were tolerated and digested at as early an age as six weeks. Introduction of cereal in the second month was not a radical step, for cereal is used to feed infants with pyloric spasm even during the early weeks of life. Strained vegetables when first fed the infant passed through the intestinal tract without any appreciable digestion. After two or three attempts the digestion of the strained vegetable was much improved. Apparently vegetables require certain digestive ferments to digest them. The production of these ferments, originally absent, seems to be stimulated by the ingestion of vegetables, with function soon following.

The "stationary weight" syndrome (failure to gain weight without other clinical evidence) followed the rapid introduction of many new strained solids. Apparently this was due to the metabolic change while the digestive ferments were being produced.

Constipation was present in about 4 of every 10 infants in the group of 166 studied, but the earlier the solids were given, the fewer the cases of chronic constipation. Although 70 per cent of the constipated infants of less than seven months of age were relieved by the addition of solids, only 40 per cent of the infants from seven to ten months of age were so relieved. The reason for this beneficial effect in the early months is apparent. Too small an amount of solids is an important cause for constipation. When this condition exists, the mother gives the infant a laxative or a cathartic. Repeated administration of these results in maladjustment of bowel mechanism so that the bowel muscles do not function until stimulated by a laxative, and the result is a sluggish bowel (atonic constipation). When solids are introduced early in infancy, there is a sufficient amount of total solids in the infant's diet, thus eliminating the cause of atonic constipation.

The study showed that the groups fed solids in early infancy had better food habits and fewer food dislikes than the groups fed solids in later infancy. The explanation for this is that the longer the infant is on breast or bottle (without solids) the more accustomed it becomes to the milk (milk habit) and the harder it is for the infant to develop a liking for solids. The early feeding of solids stimulates a desire for a variety of foods and greatly aids in improving the infant's food habits.

CONCLUSIONS

A full diet of strained solids, including strained vegetables, given during the second and third months of infancy produces better nutrition and better food and bowel habits because: (1) it contains adequate amounts of vitamins A, B, C, and D; (2) it contains iron that is needed to prevent nutritional anemia; (3) it provides bulk to the stool, eliminating an important cause for constipation in infants, and (4) it accustoms the infant to solid food early in life, thus improving its food habits.

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A CRITICAL CLINICAL STUDY OF VARIOUS INFANT FOODS

III. Fresh Whole Milk Modification Without Fat Deficiency

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IN A SERIES of articles of which this is the third we have examined clinically various infant foods. This clinical study comprises a total of 259 cases, 149 of which were fed on whole milk modified by the method herein described and 100 of which were fed whole milk modified by a maltose and dextrin carbohydrate used as a control.

The successful artificial feeding of infants consists in the adaptation of cow's milk in such a manner that the two following conditions are fulfilled.

1. The nutritional needs must be supplied by the mixture as completely as possible.

2. The formula must be adjusted so that it will be successfully tolerated by the digestive system and produce favorable digestive reactions.

The history of infant feeding is characterized by innumerable attempts to meet these conditions in a satisfactory manner. The standards for the nutritional needs have become fairly definitely fixed. It is obvious that the infant's needs are met by a formal amount of human milk of average composition. Based on a study of this natural supply and confirmed by records of successful artificial feeding, it has been established that the average infant requires about 50 calories per pound of body weight daily conveyed in a fluid volume of about two and one-half ounces, so that each ounce of food is valued at about 20 calories. This is the caloric concentration of human milk and may be assumed to be the correct physiologic standard. These calories, of course, are provided by fat, protein, and carbohydrate. Protein cannot be synthesized in the body, and the needed amount of protein of proper quality must be supplied in the food given. Human milk provides in each two and one-half ounces (50 calorie portion) about 1.0 gram of protein, and this amount meets the needs of the infant per pound daily. The fact has been established that cow's milk protein is different in quality from that of human milk, and, to compensate for this difference, it is necessary to give the infant 1.5 grams of cow's milk protein to be equivalent in nutritional value to the 1.0 gram taken in human milk. This amount of cow's milk protein is contained in 1.5 ounces of whole cow's milk and is the accepted basis for the minimum cow's milk need per pound for the artificially fed infant. To compound an adequate cow's milk formula for the infant it is therefore necessary to give daily,

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for each pound of body weight, 1.5 ounces of cow's milk diluted to two and one-half ounces with water and so reinforced by food additions that this volume will convey 50 calories. One and one-half ounces of cow's milk conveys 30 calories, so that 20 calories must be provided by the food additions. These additional calories can theoretically be supplied by fat, carbohydrate, or protein, or any combination of these elements if calories only are to be considered, since they are fundamentally energy supplies. However, since digestive conditions must also be taken into consideration, the distribution of these calories among the different food elements is of utmost importance. It is natural to turn at this point to human milk as a guide. Human milk contains over 3 per cent of fat and about 7 per cent of sugar, but less protein than this diluted cow's milk. There seems to be little indication, therefore, for adding any extra protein to the mixture. Moreover, cow's milk protein in excess of the needs is not advantageous or even desirable. Protein requires more energy expenditure for the process of digestion and the excretion of end-products, and an excess of protein in the food mixture affects digestive conditions in a manner which often proves undesirable, leading to constipation, putrefactive conditions, and high mineral excretion. On the other hand, it seems of great significance that nature provides the infant with such a high proportion of fat. Most pediatricians have always recognized this significance. Fat is of great importance as a source of the fat-soluble vitamins. Fat aids the digestion of protein and stimulates the proper assimilation of minerals, especially calcium. It also provides over twice as many calories per gram as does either carbohydrate or protein. Fat benefits digestion, and tends to control excessive fermentation and to keep the intestinal reactions well balanced, thus producing normal stools. Accordingly, many attempts have been made to reinforce the fat content of cow's milk formulas so that it will compare favorably with that in human milk. These attempts were carried out by using top milk mixtures of such strength that the proportion of fat after dilution was similar to that in human milk, the remaining calorie deficiency being made up by carbohydrate. It was found that many infants could not digest such a mixture successfully. This failure was undoubtedly due to the fact that cow's milk fat is less easily digested by the infant than the fat of human milk, chiefly because the fat of cow's milk occurs in large tough globules. Accordingly, the attempt to supply any considerable part of the needed additional calories in whole milk dilutions in the form of fat was largely abandoned, and the general procedure in artificial feeding was to provide rather more than the minimum amount of whole cow's milk and to make up the calorie deficiency by carbohydrate alone, being perforce satisfied to give only the amount of fat conveyed by the amount of whole milk used. Since infants can usually tolerate more fresh cow's milk fat than that supplied by the minimum need for cow's milk, as determined by the protein requirement, this procedure permitted the use of formu-

las which supplied from one-half to three-quarters as much fat as would be supplied by human milk. Such mixtures were found to be quite generally tolerated by average healthy infants. It was always recognized that the proportions of fat, carbohydrate, and protein differed markedly from Nature's guide, human milk, and that the mixture was, therefore, not ideal; but, since a consideration of the digestive tolerance is equally as important as the provision of a theoretically correct mixture of ingredients, this compromise was accepted as necessary.

In the meanwhile, the advance of scientific knowledge presented increasing evidence of the beneficial effects of generous fat in the diet. In the meanwhile, also, the advance of scientific knowledge has shown the way to meet this fat need without disturbing digestion. It is well known that the difficulty which the infant demonstrates in digesting raw cow's milk fat tends to disappear when the milk is processed in any way. Concentrated milks have long been recognized to be much more readily digested than fresh milk. The introduction and increasing use of dried milk and dried milk products have proved that infants have little difficulty in digesting the milk fat of milk which has been dried, especially if homogenization has been introduced into the process of manufacture. Definite proof of this is the marked success achieved in the use of several dried modified milks now generally in use. Innumerable physicians have found that infants can successfully tolerate and thrive exceptionally well on feedings containing 3 to 3.5 per cent of processed milk fat.

The inference is obvious. If enough fresh raw cow's milk fat cannot be successfully added to a fresh milk dilution so that the mixture simulates human milk in proportions of fat, carbohydrate, and protein, and if infants can successfully tolerate increased amounts of processed milk fat, the addition of processed milk fat rather than fresh milk fat is certainly indicated.

A milk modifier which embraces these principles has therefore been devised. Instead of consisting, as do the commonly used milk modifiers, of carbohydrate alone, this modifier consists of a mixture of processed cow's milk fat, mixed easily digested carbohydrates, a small amount of protein, and a significant amount of mineral salts, especially iron. By using this modifier, it becomes possible to add to the desired minimum of fresh cow's milk the needed additional calories *partly as fat* and partly as carbohydrate. The final mixture, therefore, approaches more nearly to the proportion of food ingredients found in human milk than has ever been possible to achieve by the use of usual modifiers but does not overstep the infant's fat tolerance, since the fat addition is the easily digested processed homogenized milk fat.

It was shown earlier that the basis of proper feeding for the artificially fed infant was a minimum of 1.5 ounces of cow's milk made up to a volume of 2.5 ounces with water. To this there was to be added enough additional food to provide 20 more calories, making a total of 50 calories for

each 2.5 ounces of mixture. If carbohydrate alone is added to supply this deficiency, it is necessary to add about 5 grams of carbohydrate. The resulting percentage composition of such a formula would be:

Formula A.—Cow's milk, 1.5 ounces; water, 1 ounce; carbohydrate, 5 grams

Fat	2.0%
Carbohydrate	8.7%
Protein	1.8%

These proportions are vastly different from those found in human milk, and the mixture is so high in carbohydrate that some infants would show evidence of the carbohydrate tolerance being exceeded. In many instances, therefore, the added calories are supplied partly by increasing the amount of cow's milk and partly by added carbohydrate, as for example:

Formula B.—Minimum milk, 1.5 ounce; added milk, ½ ounce; water, ½ ounce; carbohydrate, 2.5 grams

Fat	2.8%
Carbohydrate	6.7%
Protein	2.5%

Such formulas are usually well tolerated, although some infants find difficulty in handling so much fresh milk fat and the balance of food elements is far from that in human milk.

With this new modifier, 4 grams are added to the basic mixture of 1.5 ounces of cow's milk with 1 ounce of water. The resulting formula has a percentage composition as follows:

Formula C.—1 ounce of whole milk, 1 ounce of water, 4 grams modifier

Fat	3.1%
Carbohydrate	5.9%
Protein	2.1%

The mixture approaches the composition of human milk, the fat being very similar in amount. The protein is necessarily higher and the carbohydrate is therefore lower in proportion. Since only 60 per cent of the fat supplied in such a mixture is raw cow's milk fat, while 40 per cent is processed fat, it is possible for the infant to take this relatively high proportion of fat without digestive disturbance. The digestive conditions on such a feeding should approach those of infants on breast milk feeding.

The relation of the food elements to each other in the different formulas explained above is readily seen in Table I, which gives the proportions of fat, carbohydrate, and protein in the total solids of the formulas.

TABLE I

PER CENT OF TOTAL SOLIDS	HUMAN MILK	FORMULA A (1.5 OZ. MILK, 1 OZ. WATER, 5 GR. CARBOHYDRATE)	FORMULA B (2.0 OZ. MILK, 0.5 OZ. WATER, 2.5 GR. CARBOHYDRATE)	FORMULA C (1.5 OZ. MILK, 1 OZ. WATER, 4 GR. MODIFIER USED IN THIS STUDY)
Fat	30.5	16.0	23.4	28.0
Carbohydrate	56.5	69.6	56.8	53.2
Protein	13.0	14.4	20.8	18.8

In addition to providing the infant with sufficient calories, water, protein, fat, and carbohydrate, it is necessary to consider carefully the supply of minerals and vitamins. Any formula which provides enough cow's milk to meet the protein needs adequately conveys milk salts in amounts greater than those provided by human milk. Cow's milk contains three and one-half times as much mineral matter as does human milk, with the individual mineral constituents in approximately the same relation to the total ash, iron being the only marked exception. Accordingly, a dilution of 1.5 ounces of cow's milk to 2.5 ounces with water will still provide over twice as much mineral matter as 2.5 oz. of human milk. The use of this modifier further augments this supply because of the appreciable amount of milk salts contained in it. The only specific mineral substance whose content in cow's milk compares unfavorably with that in human milk is iron. Even in human milk the amount of iron provided for the infant is questionably adequate, while cow's milk is notably deficient in this element. Accordingly, this modifier has been reinforced in iron content so that a formula in which it is used contains three times as much iron as a corresponding one made with the ordinarily used carbohydrates.

Whole cow's milk provides a vitamin supply fairly comparable to that in human milk. Dilution of course diminishes this supply, especially in regard to the fat-soluble vitamins A and D. This modifier by rendering the net fat content of the formula similar to that of human milk tends to compensate for this loss of dilution, insuring a vitamin supply similar to that of whole cow's milk. The supply of water-soluble vitamin B in a formula using this modifier exceeds that of ordinary milk formulas. This is due to the fact that it is made partly from malted whole wheat grain by a process which retains to a large extent the original vitamins of the grain. Whole wheat is known to be one of the richest sources of vitamin B. This additional supply of Vitamin B is of undoubted benefit to the infant. Vitamin B stimulates appetite and growth. Vitamin C, as always in infant feeding, must be provided by dietary additions of fruit juice.

In brief, this modifier used with dilutions of whole cow's milk makes it possible to offer to the infant, formulas which contain generous protein, mineral salts, and vitamins, with increased supply of iron and vitamin B, and with a generous supply of easily digested fat similar

in proportion to that found in human milk and having a balance of food elements conducive to proper and normal digestive conditions.

PREPARATION OF MODIFIER

The materials used in the preparation of this modifier are pure, fresh, whole cow's milk, fresh cream, refined lactose, and whole wheat flour. The mixture of milk, cream, and milk sugar is pasteurized and concentrated at low temperature and then homogenized. A mash is prepared from the whole wheat flour and is then completely hydrolyzed by addition of barley malt in such a way that a definite desired proportion of dextrin and maltose is obtained. After filtration to remove fibrous matter, the resulting syrup is concentrated and added to the milk and cream together with a little iron citrate. The final mixture is dried to a powder by spraying into an atmosphere of hot air. The finished powder is then placed in cans and sealed after removing the air and substituting inert nitrogen gas. The average bacteria count of the finished product is about 3,000 per gram as determined by the standard plate method of the American Public Health Association. The bacteria have been found to be harmless spore-forming organisms, such as the hay and potato bacillus natural to fresh milk. None of these are pathogenic. The percentage composition of the product is held very close to the following typical analysis:

Butter fat	21.5%
Lactose	17.0%
Maltose	24.0%
Dextrins	28.0%
Protein	5.5%
Mineral Salts (as ash)	2.0%
Moisture	2.0%

Expressed in terms of its original component foodstuffs, the composition is as follows:

Butter fat (from milk and cream)		21.5%	
Milk solids (not fat)		7.5%	
Lactose	4.0%		
Protein	2.8%		
Ash	0.7%		
Lactose (added)		13.0%	
Hydrolyzed cereal extractives		56.0%	
Dextrins	28.0%		
Maltose	24.0%		
Protein	2.7%		
Ash	1.3%		
Moisture		2.0%	
			100.0%

The mineral elements in the ash of the modifier are approximately as follows:

Potassium	0.296%
Sodium	0.596%
Calcium	0.210%
Magnesium	0.079%
Iron	0.0036%
Sulphur	0.140%
Phosphorus	0.160%
Chlorine	0.135%

The calorie value of the dry powder is 5 calories per gram, or 150 calories per ounce, or expressed in spoonfuls

1 level teaspoonful of modifier dry, or 1.7 grams—8.5 cal.
1 level tablespoonful of modifier dry, or 5 grams—25 cal.
1 ounce by weight—18 level teaspoonfuls or 6 level tablespoonfuls.

The curd tension of various formulas made with milk, water, and modifier used in this study has varied from 3.9 to 12.7.

CLINICAL STUDY

The clinical study of this modifier was divided into two groups, the first group consisting of 99 cases, using milk, water, and added modifier. The fat infants over four months of age received from 40 to 45 calories per pound body weight; the average infants under four months of age and moderately thin infants of any age were given from 50 to 55 calories per pound body weight; and babies underweight for age were given 60 to 65 calories per pound body weight. In the 99 cases in this group the modifier was added as a carbohydrate would be added; the babies under ten pounds in weight getting 120 calories per day in the form of modifier, and the babies over ten pounds in weight getting 180 calories. Table II shows the results of this group:

TABLE II

Number of infants on modifier	99
Youngest infant put on modifier	2.0 weeks of age
Average age of infants put on modifier	2.5 months
Minimum length of time on modifier	6.0 weeks
Average length of time on modifier	16.6 weeks
Maximum length of time on modifier	7.5 months
Average weekly gain per infant	5.21 ounces
Number of digestive disturbances	7 (6.98%)

Of the seven digestive disorders above mentioned one was in the form of anorexia and six of diarrhea, two of which had an associated anorexia.

As the caloric value of a tablespoonful of this modifier is 25, 8 to 9 tablespoonfuls per day were eventually given to all infants. The one case of anorexia occurred when the modifier was increased to 9

tablespoonfuls and corrected when this was reduced to 7. The cases of diarrhea were all of the fermentative type, having 5 to 7 yellow to green semisolid stools a day. Five of the 6 cases occurred when the formula contained 9 tablespoonfuls of the modifier and the remaining one when 8 were used. All the stools returned to normal in from three to five days by the simple removal of the modifier.

Each of the gastrointestinal upsets was very carefully studied. It occurred to us that it would be possible to reduce the percentage of fresh cow's milk fat and increase the processed fat by a readjustment of the formulas. With this in view, a series of formulas (Table III) were calculated. These show that by a reduction of the amount of fresh cow's milk and by an increase in the amount of the modifier, the percentage of processed fat could be increased. Fifty infants were fed according to the formulas in Table III. The number of gastrointestinal upsets were, however, approximately the same in both groups. Nevertheless, the average gain in weight was considerably higher in the second group, and we believe that the best results with this modifier will be obtained by following the method as outlined in Table III.

The difference in feeding in this manner from that used in the first group is best explained by sample cases.

Baby J. D., aged three months, weight 12 pounds. Assuming that this baby requires 50 calories per pound body weight, the total caloric requirement would be 600.

Formula of First Group

Milk	21 ounces
Water	10 ounces
Modifier	1½ ounces (approximately 8 tablespoonfuls)

Formula of Second Group

Milk	19 ounces
Water	14 ounces
Modifier	10 tablespoonfuls

In a five-and-a-half-month-old baby, weighing 14½ pounds, requiring 725 calories a day, the difference in methods of feeding is still more clearly brought out.

Formula of First Group

Milk	27 ounces
Water	10 ounces
Modifier	8 or 9 tablespoonfuls

Formula of Second Group

Milk	23 ounces
Water	12 ounces
Modifier	11½ tablespoonfuls

TABLE III

AGE	FEEDING TABLE			PROPER MILK ALLOWANCE				PERCENTAGE COMPOSITION BY WEIGHT					PROPORTIONS OF FAT	
	WEIGHT (LB.)	NUMBER OF FEEDINGS	AMOUNT EACH FEEDING (OZ.)	TOTAL 24-HOUR VOLUME (OZ.)	WHOLE MILK (OZ.)	WATER (OZ.)	MODIFIER	FAT	CARBOHYDRATE	PROTEIN	TOTAL CALORIES	APPROXIMATE CALORIES PER OZ. VOL.	RAW FAT (PER CENT)	HOMOGENIZED AND PROCESSED FAT (PER CENT)
1 da.	6- 8	4	1	4	1	3	2 tsp.	1.4	2.7	0.9	37	9	61	39
2 da.	6- 8	7	1	6	2	4	4 tsp.	1.8	3.6	1.2	73	12	62	38
3-4 da.	6- 8	7	1½	10½	3½	7	7 tsp.	1.8	3.6	1.2	133	13	62	38
5-7 da.	6- 8	7	1½	10½	4½	6	3 tbsp.	2.4	4.8	1.6	165	16	62	38
2 wk.	7- 9	7	2½	17½	8½	9	4½ tbsp.	2.5	4.9	1.7	282	17	66	34
3 wk.	7- 9	7	3	21	11	10	6 tbsp.	2.7	5.3	1.9	370	18	66	34
4 wk.	8-10	7	3½	24½	14	10½	7 tbsp.	2.8	5.5	2.0	455	18½	68	32
2 mo.	9-11	7	4	28*	16	11	8 tbsp.	3.0	5.7	2.1	520	19½	68	32
3 mo.	11-13	7	5	35*	20	14	10 tbsp.	3.0	5.7	2.1	650	18½	68	32
4 mo.	12-14	6	6	36*	21	14	11 tbsp.	3.2	5.9	2.1	695	19	67	33
5 mo.	14-16	5	7	35*	22	12	11 tbsp.	3.2	6.1	2.3	720	20	68	32
6 mo.	15-17	5	7½	37½*	23	13½	12 tbsp.	3.2	6.0	2.2	760	20	67	33
7 mo.	16-18	5	8	40*	25	14	12 tbsp.	3.2	6.0	2.2	800	20	69	31
8 mo.	17-19	5	8	40*	27	12	11 tbsp.	3.3	6.0	2.4	815	20	72	28
9 mo.	18-21	5	8	40*	29	10	10 tbsp.	3.4	6.0	2.5	830	21	76	24

*The amount of modifier added increases the volume of daily formula by about 1 oz.

This table allows at least 1.5 gr. protein per lb. body wt. At no time until the eighth month is the raw fat as high as 70 per cent of the total. The eighth and ninth month formulas pave the way to whole milk.

TABLE IV

Number of babies on modifier	50
Youngest infant put on modifier	1.35 months
Average length of time on modifier	18 weeks
Maximum length of time on modifier	11 months
Minimum length of time on modifier	6 weeks
Average weekly gain per infant	5.62 oz.
Number of digestive disturbances	4 (8%)

Of the four digestive disturbances mentioned two were in the form of anorexia and two of diarrhea. The cases of anorexia occurred when the infants were on 11 and 12 tablespoonfuls of the modifier, respectively; the condition was corrected by simple reduction of the amount of modifier. The two cases of diarrhea were fermentative in type, there being from 5 to 7 yellow to green semisolid to watery stools a day; one infant had excoriated buttocks. Both cases occurred when the babies were receiving 11 tablespoonfuls of the modifier. By elimination of the modifier from the formula the stools became normal in from three to five days.

A group of 100 cases was used as a control. These infants were fed a mixture of fresh cow's milk, water, and a maltose dextrin carbohydrate. The results in this group are shown in Table V.

TABLE V

Number of control cases	100
Youngest baby to which mixture was given	2 weeks
Average age at which mixture was started	2 months
Minimum length of time on feeding	6 weeks
Average length of time on carbohydrate	21 weeks
Maximum length of time on carbohydrate	9 months
Average weekly gain per case	5.8 ounces
Number of digestive disturbances	7 (7%)

Of the seven digestive disorders one was in the form of anorexia and six of diarrhea, two of which had an associated anorexia.

The anorexia occurred on a formula containing 1½ ounces of carbohydrate and was corrected by simple reduction of this element. All of the cases of diarrhea occurred on a formula containing 1½ ounces of the carbohydate and were fermentative in type, consisting of from 5 to 7 green to yellow semisolid to watery stools a day. On the removal of the carbohydrate and giving a formula of one-half milk and two-thirds water the diarrhea cleared in from three to four days.

COMMENT

In analyzing the results of the first group one finds of significance the average weekly gain of 5.21 ounces and percentage of gastrointestinal upsets of 6.9 per cent. In the second group we find a weekly gain of 5.62 ounces and an incidence of gastrointestinal upsets of 8 per cent.

The obvious conclusion is that Group II did better than Group I in weight gain; however, the incidence of intestinal upsets was about the same. This shows as previously mentioned the superiority of feeding this modifier as designated in the formulas of Table III, rather than using the modifier as a carbohydrate would be used. The difference in results in the two groups is due apparently to the fact that the modifier changes both the fat and carbohydrate element of the formula and a greater percentage of processed fat is available which is apparently more digestible. The method of modifying in the second group more nearly approaches the percentage contents of human milk.

In the third or control group of babies fed with a carbohydrate modifier the average weekly gain was 5.8 ounces and the incidence of digestive upsets 7 per cent. These results compare favorably with the results in Group II.

In general, it may be said that the results in feeding infants by the method of modification herein described compare favorably in weight gain with a control group of cases fed commonly used mixtures of milk, water, and carbohydrate. By using this modifier, it becomes possible to add to the desired minimum of fresh cow's milk, the needed additional calories, partly as fat and partly as carbohydrate. The final mixture approaches more nearly to the proportion of food ingredients found in human milk. In addititon, the modifier has been reinforced in iron content so that the eventual formula contains approximately three times as much iron as is found ordinarily in milk formulas. Vitamins A and B are also found in greater quantities than in the commonly used milk mixtures.

With the use of sufficient antiscorbutic agents no manifestations of scurvy occurred.

The ordinarily used antirachitic agents were employed, and there was no greater incidence of rickets in these series of cases than in similar groups of cases reported.

CHRONIC INTERSTITIAL NEPHRITIS WITH DWARFISM

Case Report

J. W. Amesse, M.D., and Mervin H. Black, M.D.
Denver, Colo.

THE association of essential dystrophy with chronic interstitial nephritis in very young subjects, although reported occasionally in England and much less commonly in this country, must be considered among the unusual manifestations of pediatric medicine. In the

Fig. 1.—Patient compared with normal child of the same age.

most comprehensive review of nephrosclerosis in children to be found in the literature, Mitchell[1] has adequately stressed the interesting relationship between infantilism and renal rickets, and has abstracted

Children's Division, National Jewish Hospital, Denver.

76 histories, to which series he has added 2 cases from personal observation. Hunt[2] has discussed in detail the clinical and pathologic features of the disorder. Both papers are supplemented with bibliographies covering the entire period since Lucas[3] in 1883 first reported an instance of late rickets accompanied by albuminuria. We desire to report the following case of renal dwarfism now under observation in the Children's Division of the National Jewish Hospital at Denver:

M. K., female, born March 8, 1929, at Tucson, Arizona. Admitted to our hospital, February 12, 1933. The reason for admission was given as extreme malnutrition and exposure to tuberculosis. The father is alive and well, as are two sisters, ages seventeen and eighteen years respectively. The mother, aged thirty-

Fig. 2.—X-ray picture of wrists, showing normal development.

nine years, born of Jewish parentage in Russia, came to America at the age of one year. In 1921 she moved from Illinois to Arizona because of tuberculosis of the right sacroiliac joint. Five or six years ago she became a morphine addict. The mother's history further disclosed that for nine years prior to the birth of the patient she had not menstruated and that she had submitted to at least two x-ray exposures with the probable object of inducing abortion. Recent examination of the mother revealed extensive healed pulmonary tuberculosis and active tuberculosis of the sacroiliac joint.

The baby was born through cesarean section during the eighth month and weighed 3 pounds, but by the tenth day the weight had decreased to 1½ pounds. In the absence of breast milk, artificial feeding was necessary. There is a vague history of convulsive seizures at intervals during the first two years of life. Eruption of the first tooth took place before the fourth month, but a diagnosis of rickets was made shortly afterward. For the past two years the patient has given little anxiety except through her astonishing failure of physical and mental development.

Examination revealed a very small and greatly emaciated but symmetrically developed female weighing 14½ pounds. Her height was 28½ inches, stem length 17½ inches, circumference of head 15½ inches, abdomen 15 inches and chest 16½ inches. Blood pressure: 105/70. Mantoux tests were repeatedly negative. There was no overdevelopment of the genitals. She could walk hesitatingly after a few days of rest in the hospital, but a pronounced genu valgum was present without, however, any further evidence of rickets. No other pathologic condition was noted.

Laboratory findings: Hemoglobin (Sahli) 90 per cent; erythrocytes 5,870,000; leucocytes 7600; neutrophiles 4 per cent; large mononuclears 3 per cent; lymphocytes 50 per cent; eosinophiles 4 per cent; mast cells 1 per cent. Blood chemistry: Nonprotein nitrogen 37.5 mg.; creatinin 1.4 mg.; sugar 80 mg.; calcium 11 mg.; phosphorus 4 mg. (The Wassermann test on the mother's blood was negative.)

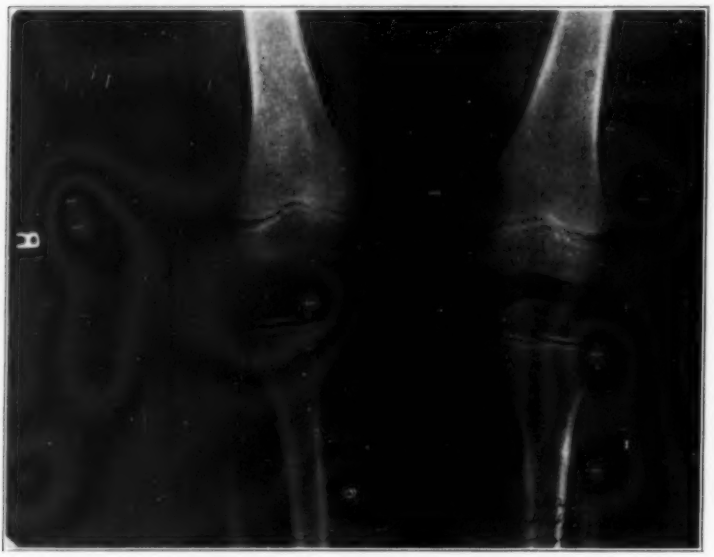

Fig. 3.—X-ray picture of knees, showing normal development.

The urine, which was quite difficult to render acid, showed albumin 4-plus and hyaline casts. Repeated examinations of the urine have been made since admission and only twice in 36 times, when the reaction was acid, were the casts absent. The albumin was never absent. Specimens of the patient's stools were never found to be strongly alkaline; digestion of proteins was apparently normal, but starch digestion was faulty and that of fats very poor. Calcium salts were present in abnormal amounts and fatty acids predominated over neutral fats.

Neurological examinations made by Dr. George S. Johnson of the Colorado Psychopathic Hospital were entirely negative. However, the psychiatric examinations showed marked retardation.

Careful x-ray studies were made by our radiologists, Dr. F. B. Stephenson and Dr. L. T. Black, who made the following interpretations: "The bones are normally calcified and the epiphyses normally ossified for the age. There are no evidences of rickets at the wrists, ankles, or ribs. The sella turcica is small but in proportion to the size of the skull. However, the clinoid processes are excessively heavy and

large. The left ulna and the left fibula show osteochondromata. The left radius is bowed more than normal. The knees show some flaring of the tibial epiphyses as noted in cases of knock knees, not necessarily rachitic. The thoracic and abdominal organs are of normal size and in proper proportions.''

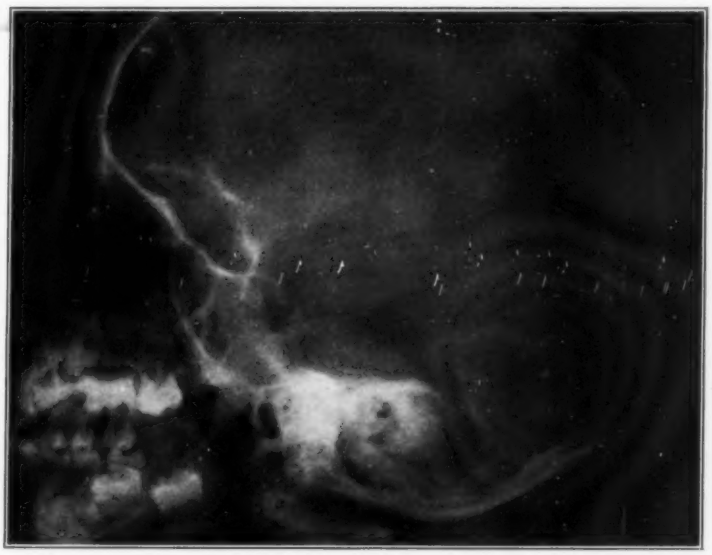

Fig. 4.—X-ray picture of skull, which is negative except for large clinoid processes.

COMMENT

The difficulty in assigning relative importance to the various agents which may have entered into the pathogenesis of this case will be apparent. All authorities agree that among the etiologic factors to be considered in dystrophic degeneration are toxins, such as those developed in syphilis or malaria or through opium or alcoholic poisoning of the mother. In this case the mother was a morphine addict. The dwarfism is so symmetrical that the secondary or Brissaud type, in which pluriglandular insufficiency is paramount, can safely be excluded. The nonprotein nitrogen and the creatinin of the blood are moderately increased, but a disturbed relation between calcium and phosphorus is not shown. The most common symptom of renal rickets, genu valgum, is present, and the deformity has been much exaggerated during the past two months since the child's improved physical state permits more activity.

While further evidence of rickets is absent, it has been recognized since the earliest observations of such conditions were recorded that the bone changes and the resulting deformities of this disease do not appear until relatively late. Mitchell[1] gives the average age of onset

in 32 cases as five years and two months, and so many develop the syndrome at puberty that it is frequently known as the rickets of adolescence. Lathrop[4] maintains that roentgenograms may be consistently negative for rickets in well-defined cases, and others consider the skeletal changes as quite independent of that disease.

SUMMARY AND CONCLUSION

A case of renal dwarfism with some unusual aspects is presented. Whether the kidney affection is of prenatal origin or was developed after birth cannot be determined. The retardation in growth and development has been so proportionate and the congenital changes have been so inconspicuous that congenital inactivity of the gonads or other endocrine structures need not be seriously considered, particularly in the absence of neoplastic invasion.

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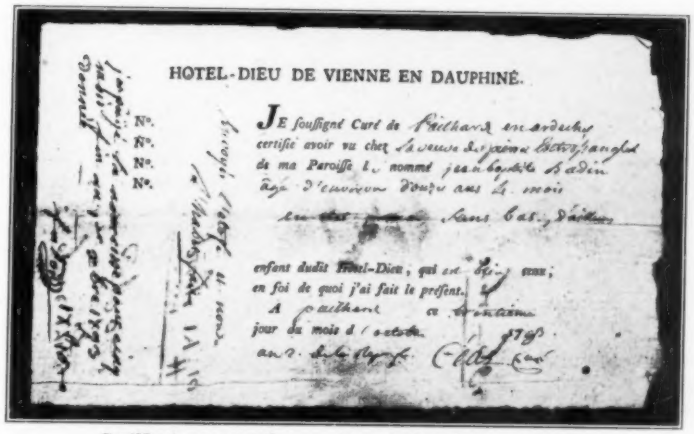
ANTIQUES OF PEDIATRIC INTEREST

T. G. H. Drake, M.B., F.R.C.P.(C)

IN THE first certificate, dated February 4, 1780, the Recteurs of the General Hospital of Saint-Esprit and St. Jacques, of the city of Marseilles, certify that one Marie Chaix is nourishing and rearing in her home an illegitimate child, aged seven years, who was placed at

NOUS ſouſſignés Recteurs de l'Hôtel-Dieu, ſous le titre de l'Hôpital-Général Saint-Eſprit & St. Jacques de Galice de cette Ville de Marſeille ; Certifions & atteſtons que l'nommé Marie Chaix du lieu de Largue les Dauon nourri & élevé chez elle un enfant naturel de cet Hôpital, âgé de Sept ans appellé Pierre George ainſi qu'apert au regiſtre V fol. 604 — Fait à Marſeille au Bureau dudit hôpital le quatre Janvier 1780



HOTEL-DIEU DE VIENNE EN DAUPHINÉ.

Nº. Nº. Nº. Nº.

JE ſouſſigné Curé de Vaulnaveys en Graisivaudan certifie avoir vu chez la veuve de Jacques Bertrand de ma Paroiſſe le nommé Jean Baptiſte Badin âgé d'environ Douze ans 4 mois en bon état ſans Gal. d'Vaulnaveys enfant dudit Hôtel-Dieu, qui est Chrétien; en foi de quoi j'ai fait le preſent. A Vaulnaveys ce vingtième jour du mois d'octobre 1785. an de Notre Seigneur.

Certificates concerning nursing of illegitimate children.

From the Department of Pediatrics, University of Toronto, and the Hospital for Sick Children, Toronto.

nurse by that hospital and in whose registers are entered particulars of the child. The second document certifies to the Hotel-Dieu of Vienne in Dauphiny that the village priest of Pailhard has visited an illegitimate child, aged about twelve years and four months, pertaining to that hospital, who was being cared for by a widow; and that the child was in good health at the time—October, 1793. Marginally, the priest asks that material and not finished clothing be sent, and the secretary of the hospital notes that he has paid the nurse for five months the sum of 17½ livres, an amount equivalent in present-day purchasing power to about 70 French francs.

Through experience the French hospitals had found that it was cheaper to place infants with nurses in their own homes than to attempt to rear them in the hospitals.

The payment for nursing varied with the age of the child. The first year, while the infant was being wet nursed, was the dearest; the nurse's fee usually remained at a somewhat lower rate from the second to the seventh year, and from the eighth to the twelfth year the fee depended on the amount of work the child was able to perform. In addition to money payments, some hospitals clothed the child until the end of its fourth year, and others until the end of the seventh year.

Schedules of wet nursing fees at various times, taken from various sources, are as follows:

In 1717, a Bourgeois of Viens records in his diary the payment of 3 livres (francs) per month for the wet nursing of his daughter in the nurse's home.

In her diary, the daughter of a Conseiller of the parliament of Paris writes that in 1747 she paid 9 livres, in 1754, 8 livres, and in 1760, 6 livres per month for the wet nursing of three successive children in the nurse's own home.

In 1802, in reply to a letter of enquiry from the mayor of Angers, the mayor of a neighboring town states that their schedule of fees for wet nursing is 5½ francs per month from birth to the age of two years, and from that time on 4¾ francs per month.

In 1823, the city of Paris paid the wet nurses 7 francs per month for the first year of the child's life, 6 francs during the second year, 5 francs from the third to the sixth year, and 4 francs from that time until the twelfth year.

In 1834 in France, the total cost of rearing a child in the care of a wet nurse from birth to its twelfth year varied in different districts from 800 to 1,300 francs.

A bill from the "Grand Bureau de Nourrices sur Lieux, fondé en 1825 par Mme. Quost," dated Paris, 1880, itemizes a wet nursing account thus:

For the nurse's first month 40 francs.
For the expenses of transporting the infant 30 francs.
The bureau's fee 7 francs.

Critical Review

DISORDERS OF INTERNAL GLAND SECRETION IN CHILDREN

FRITZ B. TALBOT, M.D., BOSTON, MASS.

THE review last year presented in as simple form as possible the reviewer's interpretation of the pertinent facts then known. Since then, several significant articles have appeared, and out of the enveloping fog some very definite landmarks and lighthouses have materialized to help the searcher for truth to steer his course.

Although many records of basal metabolic tests appear in the literature, it is unfortunate that their value is greatly reduced and perhaps entirely cancelled because the records give only the heat production in terms of "per square meter of body surface" and fail to give the *total heat production*. To make matters worse, the metabolism per unit of body surface is recorded in deviation per cent without stating what formula is used to obtain the surface area of the body, or what standards the metabolism of the subject varies from. The reviewer makes a plea that all records of basal metabolism always should record the total heat production. A brief review of the present practice in interpreting the metabolism of childhood appeared in the July, 1933, Czerny Festschrift issue of this Journal.

It has not been possible to discuss the basal metabolism data in the reported endocrine cases because it is only recorded in plus or minus per cent. The reviewer had the privilege of seeing the original data of some of the important cases reported and found that the data as presented led to quite a different picture of the progress of the disease when the metabolism was charted in terms of total heat production and compared with the expected heat production for the height and for the weight.

THE INTERRELATION OF GLANDS

One is impressed on reading the endocrine literature by the number of papers which still publish beneficial results from the use of this or that gland extract in "polyglandular syndromes." Since accurate diagnosis of such conditions is not yet possible in most cases, such reports should be considered with healthy but reasonable skepticism. Aub says, in his Presidential Address before the Association for the Study of Internal Secretions in 1932, "In recent years, at many clinical meetings the nihilistic point of view in regard to treatment has been actively championed. This point of view did much good by eliminating that which was false and unproved, and an intelligent skepticism is always most valuable, but the reaction has gone too far."[3]

Evidence has accumulated which shows the intimate interrelation of the endocrine glands. Cushing says, "Out of all the present welter of discovery relating to the internal secretions, it becomes increasingly evident that the pituitary gland holds a dominating position in the endocrine series and exercises direct or indirect control over an

unsuspected number of biochemical processes of utmost importance to the economy of the body and should one venture to single out, from many, those particular steps that in recent years did most to accelerate our progress, they were the discovery in the anterior lobe of the two inseparable hormones of growth and sex.'"[6] These will be referred to again in the section discussing the pituitary gland.

Thyroid Gland.—Since endemic goiter is attributable to a diminished or deficient supply of iodine, it has come to be considered as a deficiency disease—a deficiency of iodine. It has been recently shown that the hyperplasia which represents a stage of iodine deficiency can be brought about in animals, at least, by diets rich in either calcium chloride or sodium chloride.[10] The practical inference is that where iodine is lacking and cannot be replaced thyroid hypertrophy would be increased by the liberal use of chlorides in the diet. Salt should therefore be used sparingly by persons with iodine deficiency.

Hypothyroidism.—Recently attention has again been drawn to the work of Mason, Hunt and Hurxthal[13] who found, mainly on adult subjects with hypothyroidism and a low basal metabolic rate, that when the blood cholesterol was higher than 200 milligrams per cent they were benefited by thyroid medication. Bronstein[5] studied twenty-five normal children and found the average cholesterol values 190 milligrams per cent. He found an increased cholesterol of 277 to 782 milligrams per cent in twelve children with hypothyroidism. These values were lowered by thyroid therapy. On the other hand, the literature cites numerous cases with hyperthyroidism in which a low cholesterol was not present despite a very high basal metabolic rate. Since abnormal cholesterol figures are reported in other conditions independent of the rate of heat production, these findings should be held under advisement until further data are available. The reviewer depends on the clinical findings plus the rate of metabolism in the diagnosis and treatment of hypothyroidism of children.

Hypothyroidism without myxedema is commencing to attract attention in the literature. Youmans and Rivan[18] have described in adults a group of symptoms which they think should suggest this condition, viz.: constipation, nervousness, poor emotional control, lack of energy, vague pains localized in various regions. These patients also have a low metabolism. If the symptoms and metabolism respond to thyroid therapy, the patient falls in the group of hypothyroidism without myxedema. If not, the low metabolism is due to some other physiologic process. The reviewer has reported briefly a similar group found in girls, principally between the ages of fifteen and seventeen years, with more obscure symptoms but with definitely low metabolism according to our present standards, who were markedly benefited by the use of thyroid. They are still being studied to determine exactly where they belong in the scheme of disorders of metabolism.

Pituitary Gland.—According to many authorities the pituitary gland holds a "dominating position" in the endocrine series. It is known to contain separate hormones of growth and sex, and the recent work of Evans[7] also reports an adrenalotrophic hormone, and a hormone which influences the sugar metabolism—a lactogenic hormone, and a thyreotrophic hormone. The significance of these new hormones to human life will not be clear until more is known about them. Cushing[6] draws attention to gross and microscopic changes which result from "withdrawal or increase of the two principal hypophyseal hormones sepa-

rately." Prompt shrinkage takes place in the gonads, the adrenal cortex, and thyroid after hypophyseal extirpation in the dog and rat, while hyperplasia follows injection of the growth hormones. Since the clinical effects of chromophobe adenoma are comparable to the former laboratory experiment, one finds atrophy of the same glands in this condition and in acromegaly (hyperpituitarism) there is a corresponding hyperplasia.

Although an active growth hormone has been prepared, it is not yet available for clinical practice, nor is it certain that it will give universally good results comparable to those seen in animals. "None of the commercial preparations" which are supposed to be active "contain more than traces of growth-promoting substances even when extracted and injected into suitable animals."[15] Harvey Cushing's classical article[6] on dyspituitarism and Tracy Putnam's presentation of the present status of diseases of the hypophysis[15] both should be read in the original. They are quoted freely in this review.

The human hypophysis (pituitary) consists of two lobes, the anterior and posterior. Cushing prefers to call the anterior lobe the adenohypophysis and the posterior lobe the neurohypophysis, according to the terminology of Berbleinger. This terminology will be followed here.

The neurohypophysis is the site of the formation of pituitrin. Damage of this part of the pituitary does not cause diabetes insipidus. This symptom comes from injury to the hypothalamus and with it may be associated obesity, gonadal atrophy, and somnolence. It is difficult to understand why this is so, since the polyuria characteristic of diabetes insipidus is promptly relieved by the injection of pituitrin.

The symptoms of obesity, gonadal atrophy, and less frequently somnolence, which are frequently called Fröhlich's syndrome, can be produced by injury to the hypothalamus, yet the sex hormone is known to be in the adenohypophysis. This is another inconsistency which needs explanation. Attwell[2] after a critical study of the literature concluded that Fröhlich's syndrome is not a disease of the pituitary. On the other hantl, removal of the anterior part of the pituitary—the adenohypophysis—results in genital atrophy or infantilism. Tumors do not arise in the neurohypophysis.

All the diseases of the adenohypophysis are, so far as is now known, due to one of three kinds of tumors—*chromophobe adenoma, acidophilic adenoma,* and *basophilic adenoma.* The chromophobe adenoma secretes no hormone and the symptoms of hypopituitarism resulting from it are due solely to destruction of the normal glandular elements by pressure. The acidophilic adenoma is responsible for the growth hormone, oversecretion of which causes gigantism and acromegaly. The basophilic adenoma is rare and may secrete the sex principle. These adenomas may be associated with abdominal obesity, impotence or amenorrhea, glycosuria, hypertension, and fractures in their later stages. Hirsutism may or may not be present.

Chromophobe Adenoma.—The symptoms due solely to new growth and pressure are characteristic of chromophobe adenomas but do not appear until the later stages of acidophilic or basophilic adenomas. These tumors differ, therefore, in that the former has no symptoms at first, while the latter have initial symptoms due to excessive secretion

of their individual hormones. In the later stages when pressure and destruction take place, the symptoms of all three are affected accordingly. With increasing extension of pressure, the optic chiasm which lies above the hypophysis becomes involved, causing limited fields of vision and eventually blindness. Further afield, the hypothalamus when involved causes the train of symptoms connected with it. If sight becomes impaired, operation is necessary to preserve vision. Cushing has found on removal of the soft expanding chromophobe adenoma that the relief of pressure on the surviving normal gland substance has in some cases allowed the resumption of normal function.

Acidophilic Adenoma causes gigantism so long as the epiphyses are open and acromegaly results after they are closed. The giant reported by Behrens and Barr[4] is a boy who at thirteen and one-half years attained a height of seven feet four inches (221.5 cm.). If this type of adenoma progresses to a size which compresses the normal gland substance, sex and other functions will be interfered with. X-ray has been used with presumable success on this type of tumor by Cushing. This treatment has not yet been used in a large enough number of cases to evaluate its importance. At this writing, it gives hope of a rational method of procedure in a disease which previously had no treatment.

Basophilic Adenoma.—Although the sex hormone may originate in the basophilic cells, there is evidence that it might come from elsewhere. This question will have to be settled before a clear picture of all the activities of the hypophysis can be obtained. Cushing's[6] description of the basophilic adenoma, however, has made a picture which the clinician can readily recognize. Since very few cases are recorded in the literature, it is not possible to say if this is a disease characteristic of childhood. The youngest recorded case was fifteen years old. The disease is characterized by adiposity which spares the extremities, hypertension, impotence or amenorrhea, and fractures. Hypertension is also found in hyperplasia of the adrenal cortex and other conditions. It may be contrasted with the lowered blood pressure found in hypopituitarism of chromophobe adenoma.

The obesity of hypopituitarism does not yield to any known extract of the hypophysis.[2] Kenyon reports successful treatment of these types of obese cases by regulation of the diet.[12]

The Laurence-Moon-Biedl Syndrome was reviewed by Reilly and Lisser.[16] It is characterized by dystrophia adiposogenitalis, atypical retinitis pigmentosa, mental deficiency, familial occurrence and skeletal abnormalities, most frequently polydactylism and syndactylism. The writers emphasize that this disease "necessitates family occurrence." They thought two of their patients improved with endocrine therapy.

Parathyroid Glands.—The parathyroids supply a hormone which regulates the supply of calcium in the circulating blood and influences the phosphorus level. Complete destruction of the gland results in tetany and death unless the calcium level is maintained either by the administration of calcium or a potent extract of the parathyroid gland (parathormone of Collip).

From the clinical point of view, acute tetany is rapidly relieved by calcium chloride, but when it is due to hypoparathyroidism the cause

of this symptom is not reached without the use of parathormone. This hormone should be used with care as its dosage has not been completely established for all ages of childhood.

Hyperparathyroidism (Von Recklinghausen's Disease, Osteitis Fibrosa Cystica Generalisata).—This condition has been critically reviewed from the pathologic point of view by Jaffe.[11] The article deserves careful reading by anyone interested.

The symptoms consist of pain, bone tenderness, deformity, tumor, and spontaneous fractures of the bones. Polyuria and polydipsia are present in most cases. Associated with the increased urinary output are hypercalciuria and hyperphosphaturia. This results in decreased muscle tone, constipation, and depressed feelings. Sometimes a parathyroid tumor can be detected by the physician, but it is surprising how often this observation is lacking in the recorded cases. This is probably due to the small size of some of the tumors. The disease is usually first suspected by the x-ray findings and the diagnosis is made from the chemical examination of the blood.

Albright[1] has summed up the results obtained on ten cases from whom parathyroid tumors had been removed and seventy-three cases from the literature. He finds that the amount of circulating calcium and phosphorus is extraordinarily constant. In the adult the calcium range is 9.5 to 11.5 milligrams and the phosphorus 3.8 to 4.5 milligrams. This constancy is made possible by drawing on the calcium and phosphorus reserve in the skeleton when these salts are lowered in the circulating blood, and redepositing any excess when the salt content becomes too high. The skeleton acts in this way as a reserve station which keeps the circulating calcium and phosphorus constant. The serum calcium may be as high as 13 milligrams and the phosphorus as low as 3 milligrams in a characteristic case.

Demineralization of the skeleton may involve practically the entire skeleton but changes are most pronounced in certain bones or bony parts. The long tubular bones show the greatest degree of change and these are closely followed in frequency by the spine, sacrum, pelvis, skull, jaw bones, and thoracic flat bones. The teeth are not affected.

Albright found a relationship between hyperparathyroidism and kidney stones, as well as secondary kidney changes simulating Bright's disease. When a positive diagnosis of hyperparathyroidism is made and confirmed by the chemical laboratory, the tumor should be sought by the surgeon until it is found. If the chemical laboratory says that it is not hyperparathyroidism, that is the final word despite clinical symptoms.

Adrenal Gland.—The adrenal medulla seems to be intimately connected with heat loss from the body.[17]

Adrenal Cortex.—Since the isolation of the hormone cortin (Swingle, Pfiffer, and Hartman) and the demonstration of its dramatic effect on Addison's disease, a large number of physiologic investigations have appeared in the literature. The adrenal cortex is essential to life. When it is destroyed there is an extreme fall in body temperature, a marked loss of weight in dogs. These symptoms can be overcome by injections of cortical extract.

Tumors of the adrenal are often malignant adenomas. The characteristic symptoms are hypertension, hypertrichosis, deviations of the

secondary sex characteristics such as masculinization of women. Tumors are sometimes associated with precocious sexual development and pseudohermaphroditism, especially in the female.

Although *adrenal insufficiency* is rarely seen in young children, the possible applications in the future to pediatric problems justify a brief discussion of it here. Hartman[9] says that in cortical insufficiency asthenia develops insidiously and is the first symptom to appear. This weakness was shown to be due to involvement of the muscular tissue itself. The circulation soon becomes involved and in later stages the heart action may be feeble and the blood pressure low. Finally, the function of the kidney becomes weakened and fails. The energy metabolism is lowered and can be brought back to normal by the administration of cortin; it cannot be raised above normal level by this hormone. Cortin is essential for growth and when absent the resistance to toxins is diminished. It apparently has some beneficial action on Vitamin B and C. Pigmentation of the skin, as is seen in Addison's disease, seems to be due to lack of cortin and to be benefited by its administration. In adrenal insufficiency the blood sugar is frequently low. Hartman also has reported a new hormone called "cortilactin" which influences the secretion of milk in rats.

The data given above is confusing for the practicing physician but is of extreme interest to the physiologist. Today this knowledge has no practical bearing on pediatric problems, but it has opened a door which promises many possibilities for the future.

Sex Glands.—Novak and Long[14] made a survey of the tumors of the sex glands and found that granulosa cell tumors of the ovary have a feminizing tendency due to the production of folliculin. Arrhenoblastomas have a defeminizing tendency.

The *ovary* is activated by the sex hormone of the adenohypophysis thus stimulating the maturation of the graafian follicle. This starts the ovarian hormone called theelin by Doisy—folliculin or estrin by others. Theelin, therefore, favors menstruation. Progestin (corporinlutin) is then formed to stimulate the growth of the endometrium during the second half of the menstrual cycle. Theelin then inhibits the sex secretion of the adenohypophysis and menstruation takes place.[8] Theelin is apparently now available in physiologically active preparations and progestin is not.

Prolan is found in the blood and urine of pregnant women ("Aschheim and Zondek's Test for Pregnancy").

Although it has been shown that there is a definite interrelation of the various glands in the endocrine system, it is not clear in most cases just what that relation is. Attempted therapeutics would be simplified enormously if one could answer the old and simple conundrum "which came first, the hen or the egg?" As in other fields of medicine the best results can only be obtained by correcting the cause. Little can be said for treating the symptom alone. It seems probable that as knowledge progresses to the point where the secondary effects of primary glandular overaction or underaction are completely understood that the term "polyglandular syndrome," as it is used today, will disappear from the literature and be forgotten as are the miasmas of the past.

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American Academy of Pediatrics

Proceedings

THIRD ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

MONDAY AFTERNOON SESSION
JUNE 12, 1933

Round Table Conference on Blood Disorders Characterized by Bleeding

Leader: Dr. Thomas B. Cooley. Assistant: Dr. Heyworth N. Sanford.

The meeting was called to order at 2 P.M. by the Chairman, Dr. Thomas B. Cooley, Detroit.

DR. COOLEY.—We cannot cover all the disorders of the blood in any one round table discussion. Last year we talked about the anemias of infancy. This year we are going to take up the disorders associated with bleeding. It is not our idea to try to tell you all about the subject. What we want to do is to lay out a framework for discussion and have you all join in.

There seems to be no very good name for this group of disorders. They are sometimes spoken of as "hemorrhagic diatheses," but that is not a particularly good expression. I like the German name better—"Blütungsübel." It seems to express our meaning better than any term in common use with us.

Of course, not all of these diseases are, strictly speaking, disorders of the blood, but when we are considering the hemorrhagic disorders, though they have widely differing etiologies, the resemblances in symptomatology make it simpler to group them together.

Any consideration of the bleeding disorders requires some conception of the blood clotting mechanism, which is so often involved in hemorrhagic states. I shall try first to lay some foundation for discussion of that process.

The ideas about the clotting mechanism are, as you know, still quite confused. There are plenty of theories as to how clotting takes place, but the problem is not settled and some of the theories are quite contradictory. Some are complicated and hard to understand. The reason for the multiplicity of theories is doubtless that we have not yet sufficiently accurate methods for studying many of the questions involved. Problems of colloid chemistry and physicochemistry are encountered which are still not very well understood and not susceptible of convincing demonstration by present methods.

The principal differences in the theories depend on whether the clotting process is looked upon as a series of chemical reactions, or a group of physicochemical phenomena, or a combination of these two, or whether there is a ferment action or something analogous to it involved. There also is not complete agreement as to observed facts, and there are some generally recognized facts not explained

by any of the theories. Some of the theories are too elaborate to attempt to go into in a meeting of this kind.

Shown on the slide is what one might call the classic theory in its simplest form. It is quite generally agreed, I think, that, as I have shown in the chart on the slide, there are present in the blood as it circulates prothrombin, calcium and fibrinogen, and probably a small amount of the lipid cephalin, and that the fluidity of this mixture is maintained by something for which we may use the term antithrombin, without too great certainty as to its precise nature.

When the blood is shed, changes take place which are represented on the lower part of the slide, and which probably are started by the disintegration of the platelets. We agree that they contain cephalin, probably an additional amount of prothrombin, and therefore add these to the shed blood as compared with the circulating blood. The clot, the fibrin formation itself, is almost universally agreed to be due to a combination of thrombin and fibrinogen. Whether this is an actual chemical reaction or whether it is a physicochemical adsorption process is another matter. The classic theory in its simplest form is that when blood is shed the platelets become agglutinated, and undergo disintegration with the liberation of cephalin, which in the presence of calcium (probably serving as a catalyst) converts prothrombin to thrombin. Thrombin and fibrinogen unite to form fibrin, which is deposited as a network of long needles, enmeshing the corpuscles. Ultimately this mass of fibrin needles and corpuscles contracts, producing the firm clot and extruding the serum.

This diagram does not show some of the more recent developments of this theory, such as the formation of an inert "metathrombin" by a union of thrombin and antithrombin, and some other anticoagulant reactions which Howell has brought out. It is the emphasis put upon the anticoagulants that chiefly distinguishes Howell's ideas of clotting from those of some other workers. His theories would make a very complicated diagram, and at present they are hardly sufficiently proved to have important clinical application. It is fairly clear, however, that there must be in the blood one or more substances having an anticoagulant action and that serve to keep the blood in fluid form during its course in the circulation. How one may suppose they exert that action must depend on whether one accepts the idea of the clotting process as a train of purely chemical reactions, including chemical neutralization of the anticoagulant factors by products of platelet disintegration, or whether one agrees with the physicochemical explanation of the upsetting of the delicate equilibrium of a balanced colloid complex by the introduction of the new factors introduced from the platelets.

Bordet has been one of the important workers in the study of clotting, and his theory deserves mention. (Slide.) He makes use of a different terminology, derived from the old idea of coagulation as a ferment action, though he does not subscribe to that idea. For prothrombin and cephalin he uses the terms "serozyme" and "cytozyme," and thinks they unite in the presence of calcium to form thrombin. He lays especial stress on contact of the blood with a foreign surface in the wound (or in the test tube). The importance of this contact is unquestionable and is the reason for the use of paraffined tubes in the laboratory to minimize clotting. He postulates a "prosserozyme" which in our terminology would be "pro-prothrombin," which in contact with a foreign surface in the presence of calcium becomes serozyme; then serozyme and cytozyme form thrombin, which unites with fibrinogen to form fibrin.

Mills, of the University of Cincinnati, has busied himself with the clotting problems for a long time, and has taken up and developed the ideas of the Englishman Wooldridge. He is a careful worker, and I think deserves attention, though his theories seem not to have gained much acceptance.

(Slide.) He believes that two independent clotting processes go on at the same time. The clotting is inaugurated by a direct combination of what he calls tissue fibrinogen with the blood fibrinogen. Tissue fibrinogen is supposed to be a combination of cephalin with varying proportions of protein, and to be derived both from platelets and from tissue juices. The union of tissue fibrinogen and blood fibrinogen he believes can happen directly without any of the preliminary reactions of the classic theory, and the production of small amounts of fibrin in that way sets off the classic mechanism.

The classic theory as I presented it in the first slide seems to be the one commonly accepted in this country, and is as good as any for the interpretation of clinical phenomena.

I suppose most of you have seen articles by Kugelmass regarding his idea of measuring increased or decreased coagulability of the blood by means of a "clotting index." He seems to have been a pupil of Bordet's, and has done a good deal of work in New York on this question of measuring coagulability, both as a diagnostic procedure and as a preoperative precaution. He derives what he calls a clotting index by taking the product of the factors which favor clot formation and dividing by the anticoagulant factor, antithrombin. (Slide.) The normal prothrombin index is given an arbitrary value of one. The fibrinogen index is five-tenths, because that is not an arbitrary value. It represents the ratio of the refractive power of the serum to that of the plasma, which is normally one-half. The prothrombin index is the relation of the prothrombin time in a particular blood to that of a normal control. All theories agree in assigning to the platelets the most important place in initiating the clotting process. Kugelmass measures the platelet value by taking 200,000 as the normal count, and 50 per cent as normal disintegration in one hour, thus getting a normal figure of 100,000 for active platelets, to which he assigns a value of one in his index. The antithrombin, again, is given a normal index of one. I shall not go into the methods of determining these values, which are to be found in laboratory manuals. The values assigned give a normal index of five-tenths, from which Kugelmass allows a variation of two-tenths as within normal range.

This scheme is, I think, rather a good one—not so important in the diagnosis of the marked disorders as in minor things, such as the tendency to oozing after a tonsil operation, tooth extraction, or something of that kind. Here is a sample of how it works out. (Slide.) This was a hemophilic patient. The prothrombin index was 0.44; fibrinogen, 0.5; platelet lysis 10 per cent (index 0.2); antithrombin index 1.2. The clotting index is 0.036. The clotting time of the patient's blood was thirty minutes. Kugelmass emphasizes the very great lowering of the clotting index in hemophilia as compared with almost any other condition. It is evident, however, that in thrombocytopenic purpura with a very low platelet count the index will be fully as low.

With this rather sketchy background of the clotting mechanism, I wish to say some things about hemophilia. Dr. Sanford is to talk of some of the other disorders.

You all know that hemophilia is the great example of hereditary disease. It is also an example of sex-linked heredity, never transmitted direct by the male, but through the daughters of the male to their male offspring. Or, it may go through two or more female generations and finally appear in male descendants.

(Slide.) Here is a rather simple family tree of a hemophilic family, in which you may see how these things go. For instance, you will see in one of the lines of female descent how the trait has gone through two female generations to become manifest finally in their male descendants. This does not show some of the things that Dr. Birch speaks of, and that I have not seen mentioned elsewhere.

I should be interested to study enough hemophilic trees to see how well her statements are justified. She says the study of hemophilic trees seems to show that hemophilic males tend to have more female children, and their daughters to have more males, and that the chances are that about two out of three of these male descendants will be hemophilic. That seems to me, on theoretic grounds, rather doubtful, and I should like to see it demonstrated.

The question is always coming up whether there is any possibility, according to the laws of heredity, of hemophilia ever being transmitted by the hemophilic male to his own sons, or whether, on the other hand, there is any possibility of a female hemophilic. Apparently, so far as our present ideas of hereditary transmission are concerned, there is no possibility of the male transmitting hemophilia directly. There seems to be a remote possibility of the female hemophilic. That it has not been definitely proved to occur has been ascribed to the fact that it would involve a union of two hemophilic strains, and that the bleeding tendency in that case would be so marked that the child probably would not be born alive. This may be a plausible explanation.

Though hemophilia is not a common disease, its clinical features are quite familiar. The tendency to prolonged bleeding from slight trauma is the most striking feature, and it may be observed very early in life. There are on record plenty of cases of fatal bleeding from circumcision in hemophilic families, enough so that it has been necessary to make regulations to prevent it. The tendency to bleeding from minor trauma is not usually observed in early infancy, probably because infants are not often subjected to trauma, but it does appear fairly early in life. While it is the most common symptom of hemophilia, it is not the only characteristic type of bleeding. Bleeding into a muscle without definite trauma beyond some slight muscle strain is, for instance, not an uncommon feature. Perhaps the most striking thing in long time observation of hemophilics in the clinic is that nearly all of them in time have joint hemorrhages. First one sees them with the ordinary bleeding from trauma, and presently one finds them developing hemarthrosis in one or another joint, and this is a progressive thing with repeated hemorrhage and increasing deformity of the joint; so that in any hemophilic family one is fairly sure to find several cripples of this type.

One of the most troublesome features of the clinical picture is the tendency to bleeding from the gums. Whether the bad teeth which nearly all hemophilic children have are to be ascribed to malnutrition from lack of proper exercise I do not know, but certainly their teeth are bad and they tend to produce hemorrhage by wounding the gums. One of the difficulties in the handling of hemophilia is the bad teeth, the obvious need for their removal, and the danger of severe bleeding from the ordinary dental operations. This is perhaps the most troublesome thing in the handling of the hemophilic child in the clinic. We have at present no satisfactory method of meeting this problem, and it is a question whether to let the teeth go and have the gums subject to bleeding from trauma, or to have the teeth removed and take the chance of dangerous hemorrhage.

I need not tell you that these hemorrhages are not only serious, but quite often fatal. It is not so very uncommon to read in the paper of a child bleeding to death from hemophilic hemorrhage, or being ill for a long period. Just the other day I noticed that one of the children in the family of the King of Spain, (as you know, that is one of the hemophilic families) had been for ten days or two weeks in the hospital with bleeding which was still making trouble. The hemorrhage does not ordinarily tend to stop spontaneously until the process of repair of the wound is complete. They are not stopped by clotting. When an apparently firm clot has formed the oozing continues around its edges. Apparently, it is something like trying to make glue adhere to a wet surface.

The main feature in the hematology of hemophilia is unquestionably the delayed disintegration of the platelets. Normal platelets disintegrate rapidly after their agglutination at the point of trauma. As I have said, Bordet makes a special point of that as the thing which initiates clotting. Apparently, in hemophilia, agglutination occurs but disintegration is incomplete. There is no evidence that this is because of any abnormality of the platelets. There seems to be reason for the assumption of an inhibitory substance—an antiprothrombin. At any rate, they do not disintegrate, cephalin is not set free, prothrombin is not activated, and the result is a great prolongation of the clotting time. There is some disagreement as to methods of measuring clotting time. It seems to me quite clear that this should always be done with venous blood, to avoid admixture of tissue juices containing cephalin. It is commonly said that the hemophilic clot when formed is firm and retracts well. This is not always true, however, perhaps because of a quantitative insufficiency of thrombin entering into it. In hemophilia, the chief trouble is at the beginning of the clotting process, whereas in purpura it is at the end. In purpura clotting starts well and finishes badly; in hemophilia it starts badly and finishes well.

Aside from the clotting factors, there is no peculiarity in hemophilic blood. The corpuscles are normal and there is no anemia except the secondary anemia produced by bleeding. There is also no good evidence of abnormalities in other clotting factors than the platelets. It has been suspected that there might be an excess of antithrombin, but attempts to demonstrate this have not been successful.

A remarkable thing about the clotting time in hemophilia is the very wide variations observed within comparatively short periods, as I shall show (with slides) in a few minutes. In two observations, a few hours apart, one may get one clotting time of ten minutes, another of two hours. While it is true that prolongation of the clotting time is characteristic of hemophilia, it is not true (at least according to our observations) that one can rely on a shortening of that time as a safe indication for surgical procedures. The clotting time is a valuable diagnostic test, but not so good for prognosis.

The chief present interest in hemophilia lies in various procedures for which strong claims of therapeutic value have been put forth in recent years. We have always lacked anything like a specific treatment for this disease, especially for the prophylaxis of bleeding. Transfusion is fairly successful in checking hemorrhage. The biological anticoagulants are, in the hands of most clinicians, practically useless. Keeping the patient on a high protein diet, often recommended for all bleeding disorders, seems to be efficient in some of the minor disturbances, but has no appreciable effect in hemophilia. Its rationale apparently rests on the fact that prothrombin and fibrinogen are protein substances, and it is desirable to be sure that they are present in normal amount. A similar logic would make it seem reasonable to recommend a diet rich in nonsaturated fatty acids in conditions like hemophilia and purpura in which there is a lack of available lipid. Kugelmass urges such diets.

Some years ago Vines rather accidentally observed that the clotting time was considerably shorter during anaphylactic shock. Mills, who has written a good deal about hemophilia, has advocated strongly rendering the hemophilic patient sensitive to some foreign serum and then at bleeding times inducing a reaction by intradermal serum injection. Eley and Clifford published a paper in 1931 detailing their experiences with this treatment in several patients, concluding that the method did have some value in the handling of minor, less important bleeding, but that it was not useful in bleeding from more severe trauma or in the joint hemorrhages. So far as trials of it in our clinic have gone, we have not satisfied

ourselves of any real effect. It is an easy treatment to carry out, and deserves consideration as one of the possibilities for the routine handling of the hemophilic, as this is a condition in which one wishes to do everything possible.

Another treatment which has been in the limelight lately is that of the use of ovarian extract. This is not new. It was based originally on the peculiar sex-limited heredity of the disease, and the not unnatural assumption that the sex hormone might have something to do with the immunity of the female. The new thing is the observation by Dr. Carrol Birch that the small amount of the female hormone said to be present normally in the male urine is absent from the urine of the hemophilic. She and some others have reported remarkable results from intramuscular injection of the hormone as a therapeutic agent, and I suspect that everyone who has hemophilics in his care has given it a trial, or considered doing so.

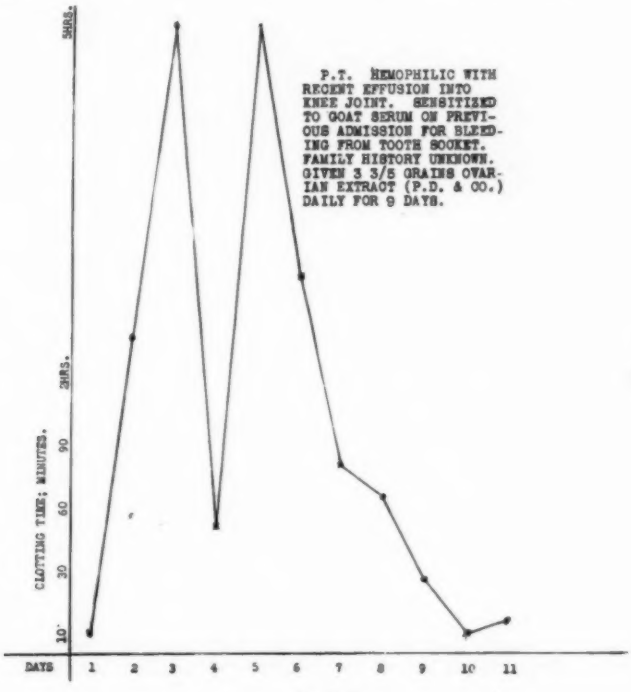


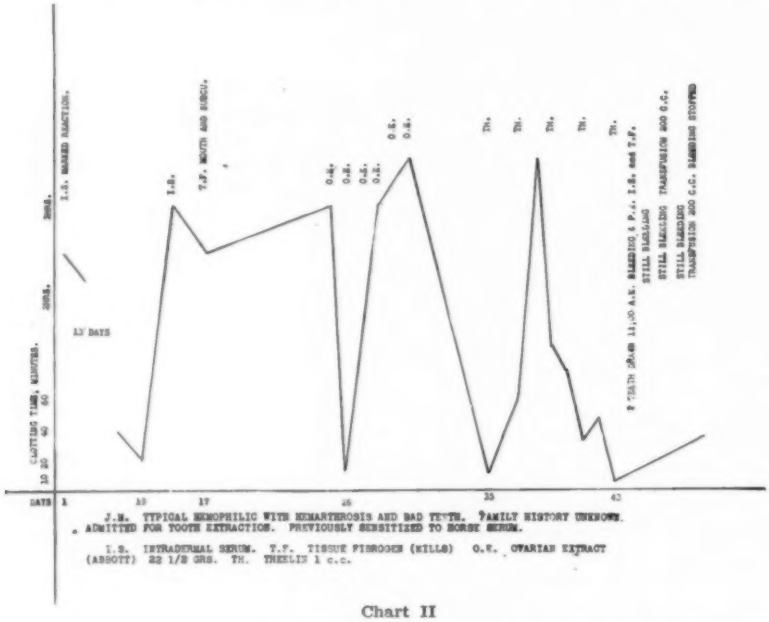
Chart I

We have been trying it on some of our hemophilics recently. I do not think that our results are at all conclusive, because we have not enough of them, but I should like to show you what we have done.

Chart I shows the curve of daily determinations of clotting time in one of our patients who came in just after an effusion into one of the knee joints. Bleeding had stopped when he came in, and we kept him to make sure that it was not going to recur, utilizing the hospital stay to observe the effect of daily injections of ovarian extract on the clotting time. The dose here was one ampule containing three and three-fifths grains of a preparation of the whole ovary made by Parke, Davis & Co. The chart shows very nicely the wide fluctuations in the clotting

time of which I have spoken—from ten minutes to five hours in this case. The chart for the first seven days looks like a malaria fever chart. From the seventh to the eleventh day you will notice that there was a gradual drop in the clotting time from ninety minutes to fifteen minutes, without the wide fluctuations. One might conclude that daily administration of ovarian extract for eleven days finally brought about a lessening of the clotting time. Perhaps it did. It did not, however, have prompt enough effect to have helped if the boy had been brought in bleeding.

Chart II is the clotting time chart from a case in which we used all methods to prepare for tooth extraction a boy who had a number of bad teeth and was having troublesome bleeding from the gums. He had also an old hemarthrosis and had previously been sensitized to goat serum. The chart shows the same wide



J.M. TYPICAL HEMOPHILIC WITH HEMARTHROSIS AND BAD TEETH. FAMILY HISTORY UNKNOWN.
ADMITTED FOR TOOTH EXTRACTION. PREVIOUSLY SENSITIZED TO HORSE SERUM.

I.D. INTRADERMAL SERUM. T.F. TISSUE FIBROGEN (MILLS) O.G. OVARIAN EXTRACT (ABBOTT) 22 1/2 GRS. TH. THEELIN 1 c.c.

Chart II

range in clotting time seen in the first one, but with a tendency to remain high for longer periods. After a period of preliminary observation during which the effects of intradermal serum and "tissue fibrogen" (a preparation advocated by Mills) were tried, with negligible results, ovarian extract was administered, first a preparation of the whole gland in twenty-six grain doses, then Parke, Davis' Theelin, one ampule daily. The curve during this period resembles that in the first chart, in that after about fourteen days of the gland treatment the excursions became less wide and the time seemed to be steadily diminishing. On the seventeenth day it had come down to ten minutes, and we thought this a favorable time for the tooth extraction. Two teeth were drawn in the morning of this day. By evening there was free hemorrhage. Intradermal serum was administered, and tissue fibrogen, by mouth and subcutaneously, both without effect. The hemorrhage stopped finally after two transfusions. You will notice that clotting time determinations were not always made daily in this case. This was because

of a difficulty which we have encountered in other hemophilics, and for which I have no definite explanation. We use venous blood for these determinations. At times there is such a marked tendency to thrombosis at the point of puncture that we cannot use the vein. I think that this may be a mechanical effect of platelet agglutination at this point without disintegration.

I have not charted one case, treated before we began to try the ovarian extract. This was another in which we wished to extract teeth, and it was our first trial of the protein sensitization method. We sensitized the patient, drew two teeth, and produced a sharp reaction with intradermal serum. The child bled very badly, and needed three large transfusions to save him.

Our results with these newer treatments do not seem to have brought out much in their favor. I do not feel, however, that we have gone far enough with them to draw definite conclusions and I am inclined to try them further. It may be that we have not used large enough doses of ovarian extract. I believe that Birch has given as much as eighty grains, gauging her dosage by the clotting time. After our experiences with the wide variations in this measurement, I do not see how the dose can be satisfactorily gauged by it. We got no effect at all from single doses, and daily doses of eighty grains would be a pretty expensive method.

The present status of the therapy of hemophilia would seem to be that we have two methods for which there is enough favorable testimony so that they deserve further careful trial. We cannot, however, depend on them to prevent or to check severe bleeding, and are not safe in undertaking any surgical procedure on a hemophilic without being prepared to apply the only measure which has been proved to be reliable—transfusion. I think that we have sometimes made the mistake in transfusing for hemophilic hemorrhage of giving too small transfusions, or of not giving them early enough. In both hemophilia and purpura I believe that large transfusions are better than small ones, and I am sure that they are more effective if they are given early, without waiting to see how bad the bleeding is going to be.

We will pause here for discussion before listening to Dr. Sanford.

DR. H. B. HAMILTON (OMAHA, NEBRASKA).—My understanding is that Dr. Mills injects the serum near the bleeding point, is that correct?

DR. COOLEY.—Yes, but it depends upon where the bleeding point is and cannot always be done. It is possible only in the minor, superficial injuries, such as bleeding from scratches, etc. As a matter of fact, we have had very little occasion to treat those things.

Another thing about hemophilia is that very commonly we have bleeding from some one of the mucous membranes—the frenum of the tongue, the gums or some similiar place where intradermal injections are not practicable. The same difficulty is met with in nosebleed.

DR. MARTIN D. OTT (DAVENPORT, IOWA).—Can you make local applications for nosebleed?

DR. COOLEY.—I do not believe it would be possible. A thing we have tried with bleeding gums is to pack them with tissue fibrogen. We have never had any effect from it. One would think that putting a substance which really contains a good deal of cephalin right into the bleeding cavity might help but we have never been able to see that it did. We have had no luck with tissue fibrogen given either by mouth, by local injection, or direct local application.

DR. STERLING H. ASHMUN (DAYTON, OHIO).—I have been very much interested in this work of the Cincinnati group, having heard them discuss their

claims. A discussion came up in a meeting, as to the best method of sensitizing a child. For instance, a young baby might be sensitized to tuberculin. Since most people are sensitized to tuberculin early in life, it might be a good thing to use intradermally as the substance to which the child might be sensitive. That might be tried early in life. They also found the use of ovarian extract to be a help. We should have thought of this a long time ago since the female does not have hemophilia and the ovarian substance is the one thing she probably has that the male does not. Certain workers believe that females sometimes do have what they consider to be hemophilia.

If there has been more than one ancestor with hemophilia, the female offspring are all the more liable to have hemophilia. We should advise that hemophilics should not marry. At the Central States Pediatric Society meeting last year, the use of muscle tissue from the individual to stop the hemorrhage was reported. That would be a good source for tissue fibrogen in any individual when an operation was contemplated. If a piece of the tissue could be planted or fastened right into the wound it might help; even placing it in a tooth socket might help to control the hemorrhage. Since ovarian extract is involved, might not those cases in which the female shows a tendency to hemophilia or purpura show some involvement of the pituitary? Dr. Cooley mentioned the finding of poor teeth so constantly in hemophilics. That suggests also a deficiency in calcium metabolism as well as a capillary penetrability. We have had favorable results in preventing, or in lessening the frequency of ordinary hemorrhage in circumcision by the use of a high protein diet in the first few days of life. I am thoroughly convinced that the high protein diet does aid even in hemophilics, in lessening the danger of hemorrhage. In one case in which the capillary clotting time was four minutes, we found after circumcision no clotting whatever, until after the injection of fibrogen; then in five minutes there was good clotting and the patient made a good recovery.

DR. T. COOK SMITH (LOUISVILLE, KY.).—Of what does the proof of diagnosis in the very young consist?

DR. COOLEY.—I think in the very young infant the diagnosis is bound to be a little doubtful. On the whole, two things are probably more important than any of the others. First, the great prolongation of venous clotting time. This however, has to be measured more than once, because you might run into one of these periods where the clotting time is pretty short, like some of those I showed on the charts. Therefore, you would have to make more than one test to insure accuracy, although if the child is actually bleeding, the chances are that you will find the clotting time prolonged. Second, failure of platelet disintegration is equally important in the hematologic diagnosis and the prolonged antithrombin time, which apparently goes with the delay in platelet disintegration. While it is a somewhat difficult thing to measure, I really think failure of platelet disintegration is perhaps the best test we have of definite hemophilia. A very low clotting index is very strongly suggestive.

DR. SMITH.—Is there any experience in your clinic to show that there are female hemophilics?

DR. COOLEY.—We have no experience indicating that there are. There are some reported observations of disturbances in the clotting mechanism in females of hemophilic families but I am not aware of any evidence of true hemophilia. Dr. Gorter, what do you do with hemophilia in your clinic?

DR. E. GORTER (LEIDEN, HOLLAND).—We have had almost the same experience you have had in regard to hemophilia. We have also tried ovarian extract in the

hope it would be useful but we could not find any definite results. I have been asked, and I would like to ask you, whether a different form of preparation of the ovarian extract might account for difference in results? I feel as you do that it is very important to make large transfusions and to do so early. If you apply transfusion from the very beginning of bleeding, I think results are temporary. I think they last almost one week and then it is necessary to repeat it.

May I ask another question with regard to the disintegration of platelets? You will find in the literature a description of thrombasthenia by Glanzmann, which indicates that failure of platelet disintegration may occur in other conditions than hemophilia. Do you believe in the existence of this thrombasthenia as a cause of purpuric conditions? Would this somewhat complicate the value of the prothrombin test or the disintegration of platelets in the diagnosis of hemophilia?

DR. COOLEY.—I have no knowledge of that disease except from Glanzmann's description, so I am afraid I could not answer. I think it must be very rare. As to transfusion, I would not have you think I am not optimistic about transfusion. I think it is the best treatment we have. We use it freely and we have never lost a patient from hemophilia.

As to the preparations of ovarian extract, Dr. Birch has used a good many of these. As you noticed, we used three different ones. I do not remember that she has had definitely more favorable results from one than from another. She simply stated, as I remember, that she tried a number of preparations and she tried also some very large doses and seemed to think the doses should vary in accordance with the clotting time.

From the clotting times I charted, I do not see how you could use them as a basis for your doses, as when you see a child with a clotting time one day of ten minutes and the next day of five hours, your choice is certainly doubtful. We apparently got as good results from the preparation of which we gave somewhat less than four grains at a dose, as we did from the other preparation, of which we gave twenty-six grains or from the supposedly pure Theelin.

DR. GORTER.—Is there any confirmation by animal experimentation of the reported testicular atrophy after ovarian extract administration?

DR. COOLEY.—I have not been able to learn of any. I have inquired of men working with ovarian extract in animals but have not heard of any definite observations on this subject.

Do any of you want to go into the question of the clotting mechanism itself?

I have a feeling that a discussion on theories of clotting does not get us very far. I mean to say that the observed facts are pretty generally recognized, and that beyond that we get into a region of theory which cannot be valuable clinically. I feel the clinician may just as well rest where he is for the time being. New things are coming up all the time.

The relation of carbohydrate metabolism to clotting is one of the things which seem to be getting quite a bit of discussion in some of the foreign clinics, and out of which I have not been able to get much so far.

DR. GORTER.—Is it not possible that there is not only failure of platelet disintegration, but some more general disturbance of reticuloendothelial function?

DR. COOLEY.—We have by no means reached a complete understanding of the bleeding disorders. I think that all of us who have busied ourselves with the blood have come in recent years to feel that eventually we may find that several of the disorders which we do not understand very well are really dependent on dysfunction of the reticuloendothelium.

One of the things about the clotting mechanism which no theory explains satisfactorily is the failure of clot retraction with a scarcity of platelets. Mills, who looks on clotting as a reversible reaction, and believes that fibrin disintegrates with liberation of thrombin, thinks that the explanation may lie in this. (I do not quite understand his reasoning.) Howell says that the only suggestion he has is that it may be a matter of a quantitative lack of fibrin in the clot.

If there is no further discussion, I will ask Dr. Sanford to go on with the purpuras.

Purpuras

DR. HEYWORTH SANFORD (CHICAGO).—In the very loose classification of conditions we speak of as purpuras it seems obvious that we are dealing with a number of etiological factors, which it should not be difficult to separate. In one recent article, however, all the purpuras are thrown into one large group, without recognition of the platelets as an etiological factor, so that it is evident there is still a good deal of confusion.

It seems to me the best method of classification is to divide them into two groups: first, the thrombocytopenic type, in which the platelets are distinctly diminished; and second, the nonthrombocytopenic type, in which there is no change in the clotting factors.

In the first group, that in which the platelets are diminished, we have a primary, "idiopathic" type, in which there is no change in any of the constituents of the blood except the platelets, and various secondary forms, in which the blood shows changes due to the primary disorder. The platelets are always markedly reduced, and the bleeding time as a rule is lengthened, usually to more than seven minutes. How low must the platelet count be to cause danger of bleeding? Most writers agree that when the count falls below 100,000, purpura may develop. McLean published in 1921 a study of twenty-one cases, all of which the count was below 100,000, the lowest being 10,000.

The secondary thrombocytopenias may be subdivided again into a group in which the platelet deficiency is due to interference with marrow productivity by tumors, leucemic infiltrations, aplastic anemia, etc., and another in which infection plays the chief etiologic rôle. Certain acute infections, diphtheria, scarlet fever, influenza, and notably the streptococcus infections, are particularly prone to lower the platelets. Streptococcus foci which remain for any time almost invariably cause a marked reduction. Among the chronic infections, tuberculosis and syphilis are likely to have this effect. In this group, we are evidently dealing with conditions in which treatment must be directed to the underlying cause.

The most interesting member of the thrombocytopenic group is the so-called essential thrombocytopenic purpura, or Werlhof's disease, one of the first blood disorders to be studied. Werlhof published his description in 1735. The chief characteristics are purpura, possibly some fever, increased bleeding time and decrease in platelets. The important thing is the decrease in platelets, the primary cause of the condition. When clot formation in this type of purpura is studied with the ultramicroscope the fibrin threads are seen to be deposited, and clotting seems to proceed in the normal way, but the clot which is formed is peculiarly soft and dose not contract with separation of the serum. Consequently, bleeding continues for a longer time.

Washed platelets from a patient with essential thrombocytopenic purpura mixed with serum from a normal person from which the platelets have been removed will cause that serum to clot, while washed platelets from a normal person will cause normal clotting of the blood of the purpuric patient. These facts

are proof that the difficulty does not lie either in any defect in the patient's platelets or in anything in the plasma, but wholly in the shortage of platelets.

Deficiency of platelets must be due to one of two reasons: either the production in the marrow is inadequate, or they are destroyed somewhere in the circulation. In the secondary thrombocytopenias, defective production is probably to blame. Against this as the cause of essential thrombocytopenia is the fact that in autopsies on patients dying from this disease, we do not find evidence of disturbance or destruction of plastocytes in the marrow. Furthermore, in secondary thrombocytopenia due to aplasia or displacement of marrow by tumors, the purpura is never so severe as in the idiopathic form.

The other explanation is that of destruction somewhere in the circulation. The reticuloendothelial system, a conception for which we are indebted to Aschoff, is composed of peculiar cells found in spleen, liver, lymph nodes and other similar tissue, the spleen containing the greater proportion of them. The large mononuclear phagocytes which are known to destroy platelets are a product of this system. If trypan blue is injected into an animal these cells take it up and become "blocked." This is followed by an increase in the platelets. Cole, in 1907, developed an antiplatelet serum. If this serum is injected into an animal there is an immediate decrease in platelets unless the spleen has first been removed, in which case there is no decrease.

We are justified, therefore, in concluding that in essential thrombocytopenic purpura the platelet deficiency is due not to defective formation but to destruction by the reticuloendothelium, in which the spleen has the chief part.

This type of purpura has a seasonal tendency. It is seen more often in the spring. Again, it is somewhat more common in females, and is likely to manifest itself before the third decade of life. The fact that it is a disease characterized by spontaneous remissions probably accounts for the great variety of treatment to be found recommended in the literature.

The idea of dietary treatment is old. Willan in 1801 advised fresh air and abundant diet. Kugelmass recommends a high protein regime. Almost all of the vitamins have had their advocates. Phillips in 1931 reported platelet increase following viosterol. Cramer and Drew in 1923 reported platelet increase, and Sooy and Moise in 1926 platelet increase and remission of symptoms following ultraviolet irradiation. This has not been confirmed by later observers. Jones and Tocantins, reporting a series of cases in 1933, mention two cases they were unable to control by transfusion, in which the platelet count was increased by pituitary extract. Three interesting, carefully studied cases have been reported in which cure seems to have followed the administration of bothrops antivenom. As the patients were soldiers serving in the Canal Zone, there may have been some unrecognized factor, though the symptoms were typical of essential thrombocytopenia.

There is general agreement as to the advisability of clearing up foci of infection. Secondary purpuras are often caused by such foci, and recurrences of essential thrombocytopenia are likely to be initiated by flare-ups of infection.

Transfusion is almost universally considered the method of choice for control of the immediate attack. I was interested in Dr. Cooley's remarks about the desirability of large transfusions, because Jones and Tocantins advocate frequent small ones. They say they have had just as good results from 25 to 200 c.c. of blood injected at frequent intervals as from 500 to 1,000 c.c. at longer intervals. They say also it must be given intravenously, which is not in agreement with our experience. We think we have had as good results with intraperitoneal injections as with intravenous administration.

Finally, we come to the question of surgical intervention by removal of the spleen. While this seems logical, and most writers report favorable results, the statistics are not so good as we should like them to be. I think that Whipple's figures published in 1926 are the best. He reported results of splenectomy in eighty-one cases, most of which he had been able to follow for five or six years. Of the eighty-one patients, 50 per cent were definitely improved after operation, and of that 50 per cent, 60 per cent were permanently benefited.

There are indications for and against splenectomy. Most observers think that if it is possible to control the condition by other means, such as transfusion, this is advisable, though it is not wise, of course, to wait too long. McLean thinks that splenectomy should be performed in two types of cases; first, in those in which the bleeding is so free that the patient will evidently soon be moribund; and second, in the chronic case with frequent relapses and resultant secondary anemia which is interfering with the patient's development.

Payr, in 1931, reported thirty-four cases in which the splenic artery had been ligated. The results, though slower, were apparently very good, and the operation is less dangerous because the shock is less. There have been no reports of thrombosis of the artery. This may prove to be the treatment of choice in selected cases.

The prognosis in this type of purpura varies greatly. The patients seem to have relapses alternating with periods of comparatively good health. McLean had four deaths in his series of twenty-five, and Jones and Tocantin nine in fifty-three cases.

So much for the thrombocytopenic purpuras.

In the second large group we have the cases in which there is neither platelet lack nor any other derangement of the clotting mechanism. Certain of these have a definite etiology. Malnutrition, lack of vitamin C and other similar conditions may cause purpura. Some infections, particularly respiratory, not uncommonly have this effect, as do mechanical factors such as varicose veins, certain tumors and pertussis.

Most of the cases of nonthrombocytopenic purpura have no such definite etiology. By far the largest number of all the purpuras fall into this class, and they seem to represent different grades of the same condition. We are all familiar with the so-called purpura simplex, of which we see a good deal, and which has no symptoms except purpuric spots—large black and blue spots on the extremities, or showers of smaller spots all over the body. There may be a little falling off of appetite, usually some nervous disturbance, but that is about all. The condition lasts from two days to two weeks and then clears up. There are almost always associated allergic symptoms such as urticaria or other manifestations of the allergic constitution. Going a little further, we have the "arthritic" type, with effusion of blood into the joints and pain apparently out of proportion to the swelling. This form, though more severe, runs the same course. Then we have the abdominal type known as "Henoch's purpura," in which, in addition to purpuric spots and joint symptoms there is abdominal pain, diarrhea and vomiting and bleeding from the gastrointestinal mucosa.

Though there is no universal agreement, these forms of purpura are quite generally believed to be allergic phenomena. It is usually said there is no change in the blood elements. This is certainly true so far as the platelets are concerned. We have recently had a case of Henoch's purpura in which, in testing the clotting factors in the way Dr. Cooley has described, we found the fibrinogen decreased to less than half normal value. Lack of fibrinogen in the blood is usually evidence of some disturbance of liver function. The lack can, of course, be congenital, and it may occur in allergic states. The blood fibrinogen is almost al-

ways found diminished in experimental allergy. I was not aware this observation had been made in purpura before, but I find that Bruhl in Germany reported two cases in 1931 in which there was the same finding.

The treatment of this kind of purpura is, of course, purely problematical. Whatever you do for it might be called simply a stab in the dark. The customary thing is to put the child on a simple, nutritious diet, giving plenty of orange juice and all other vitamins and a high proportion of protein, and assuming that recovery will soon follow. I think there is a basis for that assumption, for if these purpuras are simply allergic manifestations, and there is a lack of fibrinogen in the more severe forms, that lack at least may be compensated for by the increased protein.

DR. COOLEY.—I would like to add a few words, particularly about thrombocytopenic purpura, from our own experience. In the first place, as to splenectomy, and when you are going to do it.

The first attack of purpura is the critical attack. It seems to be true, undoubtedly, that acute infections may bring on a temporary thrombocytopenic state. When you see a child in his first attack of purpura you always have to realize he may never have another. You do not want to think of extreme therapeutic measures at that time, because it may be not only his first, but his last attack.

So it has come to be a rule with us that we will not consider splenectomy in the first attack, unless we are absolutely driven to it. It may not be a chronic condition at all.

Then there is always the question, if the thing does prove to be chronic, or recurrent, how important it is to the individual patient—and that is a matter of observation. Performing splenectomy only in emergency cases, our luck has been very good. I think, with one exception, every case on which we have performed splenectomy so far, has been cured, but we have been pretty careful in how we select them. The one case we have not cured was one which we lost just a week or so ago, and it is a good illustration of the complete futility of treatment in some types of thrombocytopenic purpura.

This child came in after a first attack following a glandular infection, preceded by measles. She came in bleeding from the mouth and one ear. In the course of her stay in the hospital she developed bleeding from the intestines and kidney. Bleeding from the mouth and ear stopped after several transfusions. We were unable to stop the bleeding from kidney and intestine, and we tried everything with one exception (and that is the antivenom) that has been recommended on any apparently logical basis for the treatment of purpura.

The child was less than a year old. She had ten transfusions, about 1700 c.c. of blood.

We finally made up our minds entirely against what would ordinarily be our best judgment, to take the child's spleen out. And we did. It proved to be a very difficult splenectomy. By the way, this is a good time to say that splenectomy is not a thing to be undertaken lightly, because it is often a very serious operation.

This child's spleen, perhaps 50 per cent larger than normal, was pretty well tucked up under the ribs and difficult to get out. The child died of postoperative shock. If she had survived the operation, I do not know whether we should have put a stop to the purpura or not. That is the first splenectomy for purpura we have lost.

We have had a number of patients whom we sent home with instructions that they were to be brought back immediately if they had another attack and at least 50 per cent have never returned. We have had another percentage

that came back with rather minor bleeding so we have felt justified in not doing splenectomy. There has been a rather small number whose spleens we have removed with perfectly good results. We always feel we may get a return of symptoms for one perfectly definite reason; that is, it is perfectly possible that a supernumerary spleen may be overlooked in doing a splenectomy. We all know how rapidly they develop after the principal organ has been removed. I believe if I saw a patient with a recurrence, I should ask the surgeon to reopen the abdomen to make sure there had not been a development of a secondary spleen. We have never had occasion to do that, still I believe it would be a logical thing to do.

We have had some interesting experiences. We have seen two cases in whom bleeding was not readily stopped by transfusion: in which it was stopped by one of the biologic anticoagulants, the one we use most often and which is called "thromboplastin." We have had two cases of obstinate nosebleed in thrombocytopenia stopped by that method when transfusion failed. This is quite against what you will ordinarily see in the literature but it is not a common occurrence.

In the allergic type we have also just had our first death. The condition was interesting because I have not seen it reported. This child came in with the ordinary picture of Henoch's purpura; i.e., the peculiar type of abdominal pain, followed a few days later by purpuric skin manifestations, which went through the ordinary course. The child had practically recovered although he still had a few spots on the skin, so we thought we were justified in allowing him to go home. He apparently completely recovered at home but suddenly he developed convulsions and died. The autopsy revealed multiple petechial hemorrhages scattered throughout the brain. That is the first thing of that kind I have seen.

One more thing about the treatment of the allergic type of purpura. While we have never found anything definite, we have felt we got better results from the administration of calcium than from anything else we have done.

DR. J. A. BIGLER (CHICAGO).—Is there any relation between the decrease of platelets and the amount of types of hemorrhage you may find?

DR. SANFORD.—No.

DR. BIGLER.—The reason I asked is because in certain conditions you may have a marked reduction of platelets, down even to 10,000 and still have no evidence of purpura hemorrhagica. Thrombocytopenic purpura is due to reduction of platelets. Why do not all patients with few platelets bleed?

DR. SANFORD.—So far as I know, there is no answer. It is just one of those things one cannot explain. Of course, the idea that the condition is due entirely to platelet decrease in not acceptable to everyone. McLean was under the impression there were other factors.

DR. BIGLER.—It is certainly true that with a marked reduction of platelets, trauma has very little to do with hemorrhages. I do not believe anyone has an explanation for some of the peculiar things one observes. It is true, as you say, that there are patients who have almost no platelets at all and that some of these will go for long periods without any bleeding. There seems to be a good deal of evidence that there must be something aside from the lack of platelets which is related to the purpuric manifestions. There must be something which favors passage of the blood through the vessel walls aside from lack of platelets. The evidence for hypersplenism or hyperactivity of the reticuloendothelial system in thrombocytopenia, I think is pretty good. Here again we think it is possible that the disease is actually a disease of the whole system rather than simply of the spleen, although the spleen, being the main part of the reticuloendothelial

system, is probably the main factor in the production of purpura by the destruction of the platelets. On the other hand, it is possible that under some conditions the rest of the reticuloendothelial system is more active in proportion to the spleen than usual and that might explain the failure of splenectomy in some of the cases where it has been reported—that in those cases, the rest of the reticuloendothelial system tissue was more active proportionately.

All we know definitely is that the condition is obviously connected largely with platelet deficiency and removal of the spleen cures, or helps to cure this deficiency. Therefore, we have to lay most of the disease process to the spleen. As to the rest of the process, I think we are still in the dark.

DR. SMITH.—You said you thought a good many of these cases of purpura simplex were allergic. Have you any idea what food does it? Do you think it is bacterial?

DR. SANFORD.—It might be.

DR. COOLEY.—I have known of just one case that gave definite reactions to food.

DR. SMITH.—We had a little girl who had a rash, and ecchymosis of the skin. A physician had removed a large mass from her neck at one time. The attacks kept recurring, and for lack of something better to do I put her on a milk diet and she became much worse. I then removed all milk and she cleared up completely. I put her back on milk and she became worse, but her skin did not react to the milk test.

DR. ASHMUN.—It has been reported in the literature that the platelet count taken after a meal is raised, sometimes a hundred thousand or more, so we should avoid taking platelet counts soon after digestion of food. What is your idea relative to the modus ope andi of that? Is it due to the fact that the blood is being used in digestion and there is less going to the spleen? What is the process? If we were to treat these patients by diet would it be necessary to use any particular type of protein or just more protein than usual?

DR. SANFORD.—Kugelmass from his experiments thought any type of protein had more effect on the platelet formation than other types of food. Whipple found that liver was very efficient in promoting blood regeneration and Mackay in several cases of pernicious anemia, was able to increase the platelets to quite high figures, that is, above 400,000, by feeding liver to the patients. This would indicate that the platelet-forming tissues participate in the general improvement in hemopoietic activity produced by liver, or rather a liver diet.

DR. BIGLER.—What method of platelet count do you use?

DR. SANFORD.—I think the sodium citrate method is as easy as any. You can do it quicker than any other way.

DR. BIGLER.—Is there any such thing as a hyperplatemia?

DR. SANFORD.—I do not know.

DR. COOLEY.—There are people who believe there is, that the platelet increase after splenectomy may reach a dangerous point. I have seen some very high platelet counts but I have not seen any unpleasant results from them. There are people who believe they can happen and that there may be a tendency to thrombosis. Of course, a certain number of platelets normally go to pieces in the circulation. They seem to believe, and probably logically, that in proportion a greater number will go to pieces when the count is high and there may be

intravascular clotting. When one sees the platelets up to a million, one wonders whether that is going to happen. I have not seen anything of the kind.

QUESTION.—Have we a medical term that describes too many platelets?

DR. COOLEY.—Not so far as I know.

DR. GORTER.—I should like to ask Dr. Sanford some questions and to comment on a few cases. Have we sufficient evidence to call this form of purpura allergic? I am a little doubtful about this name, and am not sure we are justified in ascribing the condition to allergy.

DR. COOLEY.—I like Dr. Glanzmann's name, "Anaphylactoid Purpura," better.

DR. GORTER.—I should like to draw attention to another thing in regard to thrombocytopenia. I have met with several cases in which I first made the diagnosis of thrombocytopenic purpura, but in which the subsequent course showed that we were dealing with something different. Such cases may explain the occasional failure of splenectomy. They start with an attack of typical thrombocytopenia, with very little fever and no other abnormalities in the blood. They return to the clinic with more severe bleeding and more anemia. They develop neutropenia, and that goes on for a long time. On each return to the clinic they are more severely ill. I should like to know your opinion about these; whether you believe from these observations that diagnosis in this type of thrombocytopenia would be a little difficult.

I have met with some remarkable instances of abdominal purpura. One child was interesting because it came into the clinic with typical signs of abdominal purpura—no fever, severe abdominal pain, and generalized purpuric spots all over the skin. It was found that this child had an intussusception. You can understand how difficult that diagnosis would be. Such cases are not frequent but there are several descriptions in the literature of this combination of intussusception and purpura.

To show you how difficult diagnosis can be in some of these conditions I will tell you the history of another child who came in with the same symptoms of abdominal purpura—pain, vomiting, purpuric spots all over the body. There was some fever, but very little. We thought we had an intussusception, but we found a cystic tubercular gland mass in the abdomen. The purpura in this case was due to an allergic reaction to the tuberculosis. This shows how difficult the distinction may be in these cases of abdominal purpura, and I thought it worth while to call your attention to a possible combination of abdominal purpura and other conditions.

DR. COOLEY.—We have had one case in which the diagnosis was purpura for some time until we finally found a glandular mass in the abdomen and tubercle bacilli in the stool.

DR. HAMILTON.—We recently had a case that came in bleeding. We felt it was purpura; we did a splenectomy. She did not do very well, continued to have fever and again developed an exhaustive, mild bleeding.

DR. W. L. CRAWFORD (Rockford).—Dr. Gorter's remarks and Dr. Sanford's remarks about the difficulty of putting a definite allergic, etiologic factor as the cause of these things prompts me to report this case. The mother, living about thirty miles away, phoned me one afternoon that the child's ear was definitely swollen out of shape as well as parts of the face. The child had an eczema. I

told her it was probably an angioneurotic edema. A few hours later she brought the child to the office and he was perfectly normal. It recurred on the baby's cheek and lip.

Three days later the child was afebrile and had no temperature. The child later developed temperature 108°. Adrenalin was given. I have seen no definite reports of angioneurotic edema in the medulla or thermo-regulating center. I do not know how one could prove this happened but as quickly as we administered adrenalin, the temperature went down eight or nine degrees.

Again, after two or three days, the child suddenly developed distress in the stomach and the entire upper half of the abdomen became greatly enlarged. The child was in great distress and later about a quart of a chocolate-like material was siphoned off from the stomach, which reacted very strongly to blood. This recurred again two days later and on the second occasion, the child had some fever. Following this we tested the child for many things from the allergic standpoint except house dust. Results of these tests were negative.

DR. OTT.—I have not had a case of purpura under my care but certain other conditions like some of the upper respiratory infections have brought out certain points in relation to allergy. In one case of a child I could not get a sample of the respiratory secretion but I took cultures from the stool. I found that the child gave a very good epidermal reaction to these organisms. I then desensitized the patient. The patient had surprisingly good results in a few days. One case is not enough to prove anything but I think it might be a good thing to look at allergy from a bacterial standpoint rather than entirely from a food standpoint.

DR. SANFORD.—Of course, all this subject of purpuras is not clear. What I have given you is simply the usual ideas of the present time. As Dr. Gorter said, it does not work out nearly so nicely as we like to think, that these are all allergic manifestations. There have been a few cases in which work has been done to indicate that it might be that type but, on the whole, there are just as many cases where it is absolutely impossible to find any reason. I think your suggestion about the bacteriological viewpoint is certainly worth while.

QUESTION.—Dr. Gorter, in the first case you cited, of what did the child die?

DR. GORTER.—It was one of a large group of children. We did not have many autopsies. One might say it is almost a description of leucemia.

DR. COOLEY.—I have seen several such cases. Some of the writers make quite a point of the fact that one can see all grades between thrombocytopenic purpura and an outspoken aplastic anemia. There is a considerable group in which apparently there is a marrow hypoplasia. I wonder whether that would not apply to the group you are speaking of.

DR. GORTER.—Yes, I should think so. I think that in most cases of real aplastic anemia it starts, so to speak, with acute symptoms and death occurs in six weeks or so with high fever.

DR. COOLEY.—I think there is a very definite difference between what I speak of as hypoplastic anemia and aplastic anemia. I think sometimes the platelets are more involved than the other blood elements in the hypoplastic state. The pathologic pictures are very different in the bone marrow in the two conditions.

DR. SANFORD.—In answer to a question about ultraviolet therapy, the results are variable; sometimes there is an increase. Certainly in the newborn

there will be a slight increase in platelets following ultraviolet radiation but the newborn is most unstable and there is no reason to expect that the adult would react similarly.

DR. COOLEY.—It seems to me the argument for that type of treatment is not very good because in experimental animals we are not dealing with a condition of excessive platelet destruction. The difficulty in thrombocytopenic purpura is that you would not expect to be cured by any temporary or minor increase in platelet production because they are all destroyed. That seems to be true except in some secondary forms of purpura. For instance, where the marrow is crowded out by leucemic infiltration. If the productivity of what marrow is left could be increased, that might help.

Dr. Sanford, were you going to say anything about the hemorrhagic disease of the newborn?

Hemorrhagic Disease of the Newborn

DR. H. N. SANFORD.—Occasionally, in the newborn somewhere between the second and eighth days of life, we meet with a type of hemorrhage for which there is no clear explanation. The forms for which there is a definite etiology, such as infection, septicemia, trauma and congenital syphilis, have been excluded. Clinically there is nothing particularly characteristic except the bleeding. This may be from the mucous membrane of the nose or gastrointestinal tract, the cord, or the meninges. There are no other symptoms except the secondary anemia. The bleeding rarely comes before the third day, and rarely after the sixth. To judge from reports in the literature, the frequency of this condition must be decreasing rapidly. Le Queux's statistics, the earliest I know, showed an incidence of nearly 35 per cent. The last series of any note is one from Grob in Lucerne, in which he found only fifty cases in ten years.

As to the cause of the condition, every one of the clotting factors mentioned by Dr. Cooley has been reported as being affected. Whipple found a decrease in prothrombin; Schloss and Kommisky found lack of thrombin in one case, and of fibrinogen in another; Kugelmass found decreased fibrinogen. All are agreed that the platelets are not diminished. Grob found no lack of them in any of his cases.

This hemorrhagic state of the newborn must be distinguished from bleeding due to mechanical factors. Bonar found chemical evidence of blood in 30 per cent of stools from one hundred nine newborn babies. An infant may vomit swallowed blood if the mother's nipples are cracked. Hemorrhagic disease is excluded by the absence of any change in bleeding or clotting time. Rodda, in his studies of normal bleeding and clotting time in the newborn (made with capillary blood) found that at birth the infant has times comparable with those of the adult (five or six minutes' clotting and three or four minutes' bleeding time), and that the time tends to increase to a maximum about the fourth day, after which they drop to normal. If this is true, practically every newborn child is in a prehemorrhagic state. Several years ago we determined the clotting factors in a group of thirty-five newborn. We found thrombin and antithrombin a little lower than normal and fibrinogen slightly higher. If this is the rule, there must be other factors at work in the hemorrhagic state. We endeavored to find things which would alter the proportions of the clotting elements. Viosterol and ultraviolet light had no effect. The first change observed followed withholding protein and fat from the food. This was done by keeping the child from the breast for five days, giving ample salts and carbohydrates. By this procedure we obtained a distinct lessening of fibrinogen, but hardly enough to cause bleeding.

The decrease in this condition seems very striking to me. Since we have been interested in the study of the clotting factors in the last five years we have not had a single case of hemorrhagic disease in which we could make these determinations. We have had two or three brought in from outside, but in too advanced a stage.

As to prophylactic treatment, that, of course, is an obstetric problem, and I believe the lessened incidence of the disease is due to the fact that most of the mothers' diets are better. We never see it in private practice, and most mothers in dispensary groups have a well-supervised diet. Moore was able to produce a hemorrhagic condition experimentally by feeding the mother a diet lacking in vitamin B. Graham, in 1910, found that young animals subjected to prolonged anesthesia showed increase in bleeding and clotting time. The same thing has been shown in the child born after a long ether or ethylene anesthesia. As to obstetric manipulations, I have never observed that they had anything to do with producing hemorrhagic disease. Most of the cases have followed normal deliveries. Kugelmass advocates giving gelatin from birth for prophylaxis. Most babies will take gelatin readily, but it seems to me that if one wishes to administer protein, it might as well be in the form of a high protein food that the child can utilize.

In treatment of the actual hemorrhage I think that anything except blood is useless—calcium, viosterol, thromboplastin, etc., are simply a waste of time. For the past fifteen years immediate injection of whole blood has been recognized as the only effective treatment. Dr. Smith asked about mother's blood in the hemophilic. There is a feeling among obstetricians that they have better results in the hemorrhagic disease from the use of the father's blood instead of the mother's. In the past few years we have tried to determine whether father's blood, mother's blood, or "foreign" blood has the most effect on the clotting factors. From our figures it would appear that we had somewhat more effect from the foreign blood. Father's blood comes next, and the mother's blood gives somewhat the poorest results. In using foreign blood one must of course, be sure about the Wassermann test, while one does not have to worry about that so far as the parents' blood is concerned. If there is anything to an inherited or maternal tendency in the disease it might be carried over in the mother's blood. I like to use the father's blood when I can. We have had very good results from giving small quantities (10 c.c.) of father's blood intramuscularly. In severe cases we have given 50 to 100 c.c. intraperitoneally and thought we got as good results as from intravenous injection. We never give large amounts; that is necessary only in rare cases. Usually the bleeding can be controlled satisfactorily by small intramuscular injections.

DR. COOLEY.—The idea of starting with the small amounts of blood however, is a little dangerous but, of course, that has been extensively advocated. Nearly fifteen or twenty years ago, it was a general procedure and I saw several cases that made me reach the conclusion I would rather play safe and give more.

QUESTION.—Wouldn't it be better to give a transfusion and begin life less anemic?

DR. SANFORD.—My feeling is that some of these patients are very anemic. Such a child should have the blood replaced in a very short period of time. It certainly does not do any harm and I think there is everything in favor of it.

QUESTION.—What veins do you usually use in the newborn?

DR. COOLEY.—If you are particularly expert in manipulation, it is surprising what you can do in some of the smaller veins. I know one man who gives trans-

fusions in the newborn infant in the veins of the scalp but that takes practice. We use the saphenous vein more than any other.

DR. ASHMUN.—Perhaps you are familiar with Dr. Wagner's series in Cincinnati. He had 200 cases of premature infants he reported in which he used the blood as prevention of hemorrhagic disease. He has another 100 cases now, making a total of 300 cases. He gives them either the mother's or the father's blood and has not had a hemorrhagic disease develop in any one of those 300.

DR. COOLEY.—Dr. Dunham tells me they have studied a series of 1,000 newborn infants and in that series, where nothing was done for prophylaxis, there were only 3 cases of hemorrhagic disease. She very properly said, it would take a fairly large series of cases to prove results from prophylactic treatment of any kind. In other words, in the series of 300 you cite, you would not have expected more than one case of hemorrhagic disease.

DR. ASHMUN.—In view of the fact that there is such a small incidence, is it not likely that diet plays a large part?

DR. COOLEY.—Dr. Dunham was asking what I thought they might do to study that question further. She suggested the thing to do was to study the mothers.

DR. SMITH.—The premature infants would be better to receive the father's blood, according to your findings, Dr. Sanford.

DR. SANFORD.—I do not remember seeing a case of hemorrhagic disease in the premature infant. In fact, we have not had a case on our newborn service of hemorrhagic disease in the last five years. The only cases we have seen are those coming in from the outside.

DR. ASHMUN.—Do you not think they formerly classed a good many as hemorrhagic disease that were not, or that are not classed that way now?

DR. SANFORD.—I meant to mention that. You will find a lot of cases of hemorrhagic disease due to syphilis. I think the big point is that the bleeding time is almost always increased over the coagulation time. If it is increased at least five or more minutes over the coagulation time, it is undoubtedly syphilitic.

DR. HELMINA JEIDELL (SALT LAKE CITY).—Is it usually found in only one pregnancy?

DR. SANFORD.—There have been some cases reported where it occurred in more than one pregnancy but I have never seen it.

DR. COOLEY.—There is one other subject that might be worth speaking about while we are on this question, that is a procedure I suppose to be common—making clotting and bleeding time tests before operations. My opinion is that those things as ordinarily done are not worth anything and yet it gives people a feeling of safety which I do not think is warranted. If that sort of thing is to be done at all that is where this scheme of Kugelmass' of using a clot index is worth something, because it will uncover things not necessarily uncovered by the ordinary tests. When, for one reason or another, one really wants to have a definite idea whether a patient is likely to bleed abnormally after a tonsillectomy or something of that kind, I think the surgeon and the family doctor should understand that something more than just the ordinary coagulation and bleeding time from capillary blood should be used and I do believe this scheme of Kugelmass' has probably a good deal of value.

The meeting adjourned at 4:50 P.M.

Academy News

MEETING OF REGION III AMERICAN ACADEMY OF PEDIATRICS

PRESBYTERIAN HOSPITAL, CHICAGO, SEPT. 23, 1933

(Number present, 28)

Dr. H. F. Helmholz, Chairman, Presiding

Motion made by Grulee, seconded by Gengenbach that an invitation be extended to all members of the disbanded Central States Pediatric Society to attend the clinical meeting of Region III. Carried.

There was a discussion of the character of the meetings to be held by the Region in the future.

Grulee gave his opinion that the meeting should be mainly clinical.

Veeder after explaining the type of meetings held in St. Louis, suggested a one day clinical meeting by clinicians in the city where the meeting is held; one day program given over to papers or presentations by men from other cities in the Region.

Aldrich thought it was wise to determine how many cities in the Region could entertain the meeting.

Rowland states that he always liked to see the interesting cases.

Hamilton especially likes the clinical part of the program.

Irish thinks the important thing is to present practical subjects whether didactic or clinical. He does not think that the demonstration of a patient is always effective in teaching a particular point or subject.

Helmholz summarized that the meetings should be both practical and clinical; that a local committee be given plenty of latitude to draw on the entire Region for men to present the program.

Moved by Veeder, seconded by Gengenbach that the matter be left entirely to the Regional Committee. Carried.

Next meeting to be decided by the Regional Committee and Gengenbach suggested that the number of sessions at the time of the meeting is a qustion to be considered by the Regional Committee.

Veeder expressed the opinion that he would like to have the dinners, such as were held in the Central States Pediatric Meeting, continued in the Region.

Aldrich suggested that the clinical meetings be made open meetings.

Grulee thought that the business meeting should be held at the time of the dinner.

Gengenbach suggested that if the meetings be open, it would be difficult to get a place big enough to hold the meetings.

Reports of State Chairmen

Hamilton of Nebraska reported that they have organized a committee in Omaha which is advisory to the schools on all health activities. This committee is very active. It is handicapped by having no money to carry on any work. There is no activity outside of Omaha.

Carson of Kansas—no report.

Schwartz of Wisconsin—no report.

Baxter of Illinois reported that the committee in Illinois has been very active. The chief activities include first, a subcommittee appointed to contact and advise with all governmental departments having to do with Child Welfare and Child Health. This committee has secured the appointment of two members of the Academy on the advisory committee of the Illinois State Department of Health. Second, a subcommittee has contracted with all nongovernmental organizations in child welfare. This committee has made such contacts and is making some progress. Third, the committee has succeeded in the establishment of a Pediatric Section in the Illinois State Society. Fourth, the committee has made a policy to conduct all of its state activities through the channels of the regularly organized State Medical Society. Fifth, the committee has organized state-wide pediatric programs, the purpose of which is first, to stimulate the greater interest on the part of the general practitioner in both the well and sick child in order to make the general practitioner more child-conscious. Second, it is the ideal that eventually there will be no need of any child welfare organizations because of the desire to make every doctor's office a health center. The state has been divided into districts more or less corresponding to the Councillor districts of the State Medical Society. A chairman has been appointed for each district. Meetings have been arranged for and five meetings have already been held. The reception of these meetings has been most gratifying and encouraging. During the winter it is hoped to put on a similar program in each of the Branch Societies of the Chicago Medical Society.

Hill of Iowa reported that for two successive years, a pediatric program has been put on at the State Society meeting. A committee has been appointed to coordinate with the work of the State Board of Health with the State Medical Society. Education is the object of both of these organizations. Each county is being organized to appoint a committee on Child Welfare and protection. The Iowa State Medical Society maintains a speakers' bureau.

Winters of Indiana stated that they have organized similar to the Illinois state organization. They have a very close contact with the state government and the work is being definitely supported by the Governor.

Gengenbach of Colorado reported that each state has its own problems. They have only five members of the Academy but they have been able to accomplish much through the Rocky Mountain Pediatric Society and by cooperating with the various health departments. The state-wide work has been very limited except through some agencies already organized for that purpose.

Helmholz suggested that there may be danger in having pediatric sections of our state societies conduct programs for a few pediatricians and not bring these various subjects to the attention of the general practitioners attending other section meetings. At the Minnesota meeting there are several pediatric papers in each medical program.

Schorer of Kansas City reported that the pediatric club in Kansas City, composed of about 12 pediatricians, has written the entire regulations for contagious diseases and the regulations for immunization which are a part of the municipal health activities; that no clinic of any sort can be started in the county without the approval of the county medical society. This group has also sponsored and regulated the production of milk and they have gotten everything they have asked for from the authorities.

Miner of Michigan—no work has been done. Two meetings have been held.
Carey of Michigan.

Hempelmann of Missiouri.

Burnham of Ohio had written that they could not be present to report.
Meeting adjourned

Region II

Region II of the American Academy of Pediatrics held a meeting on Wednesday, November 15, in Richmond, Virginia, at the time of the annual meeting of the Southern Medical Association. There was a meeting of the Regional Board on Wednesday morning, followed in the afternoon by a joint meeting of the health officers of the southern states and the larger cities of the South. This meeting considered the reports from each of the committees appointed last year. Dr. John Rührah addressed the joint meeting of the members of the Academy and the Pediatric Section of the Southern Medical Association in the evening, on "Acute Anterior Poliomyelitis."

News and Notes

Dr. Harrold A. Bachmann of Chicago, Attending Pediatrician at St. Luke's and Children's Memorial Hospitals, died of heart disease recently at the age of 42 years.

Correction.—Remarks attributed to Dr. Alvah L. Newcomb of Chicago, at the Round Table Conference on Rheumatic Heart Disease, on page 671, volume III of the JOURNAL OF PEDIATRICS, were made by Dr. John C. McDavid of Oak Park, Illinois.

The Central States Pediatric Society held its annual meeting in Chicago, September 22, 1933. This meeting was held in connection with Region III of the Academy of Pediatrics. Approximately 200 members were present.

The session on Friday morning was held in the new auditorium of the Children's Memorial Hospital. Luncheon was served at the Michael Reese Hospital, and in the afternoon a clinical program was presented by the staff of the hospital. Friday evening a dinner was held in Pabst's Cafe at the Chicago Century of Progress Exposition grounds. At this time a business meeting of the Central States Pediatric Society was held. Saturday morning the program was conducted at the University of Illinois College of Medicine.

The business meeting of Region III was held at the Presbyterian Hospital on Saturday afternoon with reports of the various state activities. The problems connected with holding a clinical meeting each fall were discussed.

At the business session of the Central States Pediatric Society, the Executive Committee's Report included two recommendations of general interest:

"Recommendation 3. That, whereas there is now a national organization with regional subdivisions; i.e., The American Academy of Pediatrics, which to a large extent duplicates the activities so ably carried on for many years by our Society, and whereas, the Executive Committee at our meeting last year in Kansas City were unanimously of the opinion that the Central States Pediatric Society might well be disbanded, but deferred action in order that the question might receive more deliberate consideration, the Executive Committee now recommends that this Society be disbanded.

"It further recommends that the Society suggest to the Regional Committee of Region III of the American Academy of Pediatrics, (1) that its meetings be conducted as nearly as possible after the manner used by our Society in our annual clinical meetings, and (2) that the members of the Central States Pediatric Society in good standing at the time of its disbandment who are not members of the American Academy of Pediatrics, be invited to attend the annual clinical meetings of the regional subdivisions in which they live.

"Recommendation 4. That the balance of funds left in the treasury after the obligations of the Society have been paid be transferred to the Abraham Jacobi Memorial Fund, this being a fund under the direction of the Section of Diseases of Children of the American Medical Association to which all members of our Society either belong or are eligible. It further recommends that the president appoint a committee of three to audit the books of the treasurer and that this auditing committee be authorized and directed to turn over the balance after the obligations of the Society are paid, to the Abraham Jacobi Memorial Fund in accordance with the preceding resolution.

"All of the recommendations of the Executive Committee except the fourth were approved as read.

"The recommendation regarding the disposition of funds was discussed by several members. Dr. Veeder proposed that in making the transfer we specify that in order to perpetuate the name of the Society, some of the money be used to make a medal called "The Central States Pediatric Society Medal" to be awarded each year to some one for special excellence in some pediatric work. Dr. Helmholz, Dr. Neff and Dr. Grulee spoke in favor of this idea.

"A motion was made by Dr. Grulee and seconded by Dr. Helmholz that the money transferred to the Abraham Jacobi Memorial Fund be specified as the Central States Pediatric Society Fund with the suggestion that part of it be used to perpetuate the name of the Society; the manner in which this is to be done to be decided by the Committee in charge of the Abraham Jacobi Memorial Fund.

"This motion was carried.

"The original recommendation with this amendment was then approved by the Society."

The annual meeting of the **Pediatric Section of the Michigan State Medical Society** was held at Grand Rapids, Michigan, on September 13 and 14, 1933.

Dr. Thomas B. Cooley of Detroit gave an interesting résumé of the present-day conceptions of Blood Dyscrasias in Infancy. Dr. T. Wingate Todd presented a résumé of his work on Bone Age in Infancy which is being carried on at the Brush Foundation in Cleveland, Ohio. Dr. Louis H. Newburgh of Ann Arbor, Michigan, reviewed the recent advances in the study of Calcium Metabolism.

The officers elected for the year 1933-34 are as follows:

Chairman: W. A. Collins, M.D.
103 W. Burdick
Kalamazoo, Michigan

Secretary: Edgar E. Martmer, M.D.
749 David Whitney Bldg.
Detroit, Michigan.

The next meeting will be held at Battle Creek, Michigan, in September, 1934.

The regular meeting of the **Detroit Pediatric Society** was held September 6, 1933, at the Children's Hospital of Michigan.

The following officers for the year 1933-34 assumed their duties.

President:	J. A. Johnston, M.D. 2799 West Grand Blvd., Detroit.
Vice-President:	E. W. May, M.D. 1551 Woodward Avenue, Detroit.
Secretary:	Edgar E. Martmer, M.D. 749 David Whitney Bldg., Detroit.
Treasurer:	E. W. Wishropp, M.D. 5061 Woodward Avenue, Detroit.

The following appointments have been made to membership in The American Board of Pediatrics.

By the American Pediatric Society:
Dr. C. Anderson Aldrich, Winnetka, Ill.
Dr. Henry F. Helmholz, Rochester, Minn.
Dr. Philip Van Ingen, New York.
By the American Academy of Pediatrics:
Dr. Harold C. Stuart, Boston, Mass.
Dr. Borden S. Veeder, St. Louis, Mo.
Dr. Alfred A. Walker, Birmingham, Ala.
By the Section on Pediatrics of the A. M. A.:
Dr. Wilburt C. Davison, Durham, N. C.
Dr. Franklin P. Gengenbach, Denver, Colo.
Dr. Edward B. Shaw, San Francisco, Calif.

The Board is in the process of organization and incorporation. Announcements in regard to the Board will appear in *The Journal of Pediatrics* and *The American Journal of Diseases of Children.*

Book Reviews

The Diagnosis and Treatment of Postural Defects. W. M. Phelps and R. J. H. Kiphuth, Charles C. Thomas, Springfield, 1932, pp. 180.

This monograph is the best one on the diagnosis and treatment of postural defects that has come to my notice. The material as well as the manner in which it is presented and illustrated leaves nothing to be desired. It can be recommended to all students of the subject and the knowledge contained in it should have far wider application especially in the physical education departments of our schools. If only teachers of physical education realize that—

(1) The term "flatfoot" is very misleading,

(2) That forward shoulders in children is related to the prominent abdomen and is rare during the adolescent period,

(3) That there should be no attempt to localize lumbar correction in children because of the danger of compensatory defects due to flexibility,

much wasted effort as well as considerable harm would be prevented.

Chapter I on evolutionary influences will repay anyone for careful study. While one must, as the authors frankly admit they have done, draw upon his faculty for imagination when he attempts to understand the many and varied steps by which man has arrived at his present development of the upright posture with bipedal locomotion, there is no other method of analysis which so satisfactorily serves as a basis for study and didactic teaching. The reconstruction of evolutionary influences with the realization that gravity is the principal force in the maintenance of good posture with a minimum expenditure of muscular energy lay the best foundation for more detailed study and a clearer understanding of body mechanics.

On the subject of environmental influence I cannot entirely agree with all the ideas expressed by the authors. The study of this chapter gave me the idea, perhaps mistakenly, that the authors have not studied the natural changes in posture that one sees in the observation of individual children during the whole period from infancy to young adult life. While the study of many individuals in age groups yields invaluable information, it is only by the continuous observation of individuals as each grows up that one learns to predict his future development. Such study is the basis for the following suggestions:

Every normal infant is bow-legged until after he has walked for a few months. The authors suggest too early walking as a cause of bowlegs. All children go through a period of physiologic knock knee with pronation of the feet accompanied by a stretching of, or a lack of development of the heel cords which permits dorsal flexion of the feet well beyond a right angle. This stage of knock knee and pronation of the feet reaches its height at age three and is sufficiently corrected by age five or six to be of no consequence. The correction is accomplished, I think, by the development and better coordinated use of the external rotators of the thighs and of the gluteals. The authors mention both the pronation of the feet and the knock knee but do not sufficiently emphasize them as parts of normal development. Failure to recognize the physiologic nature of the normal amount of pronation in the feet of young children has given rise to the widespread practice of attempting to correct it by means of advancing and elevating the inner borders of shoe heels (Thomas heels) and worse still by elevation of the inner borders of the sole as well. These mistaken attempts at cor-

rection contribute considerably to the unnatural shortening of heel cords and very probably to the development of rigid contracted feet. In turn this shortening of the heel cords contributes the undesirable effects higher up so well described by the authors on page 15. When the child is about six years old, if pronation persists, it may be safely corrected because the child will then have lost some of his natural flexibility as well as have acquired such a degree of muscular development and general coordination that he can better distribute and utilize the effect of the correction. This argument is in line with the authors' well-defined and wise warning that posture training should not be begun too early in the child's life because of the danger of overdevelopment of certain muscle groups.

The importance of shoes and stockings is well emphasized. Anyone who has observed the deformities produced by tight stockings and badly fitted shoes, especially the shoes that are fitted or worn until they are too short, can have no doubts concerning the attention that should be given to these articles of apparel. I cannot agree with the authors' idea that "a moccasin is innocuous when worn on a normal foot." A moccasin is, I am certain, the only form of shoe for normal infants until the full development of skillful coordinated walking which does interfere with the best development of the muscular power and functional skill of the feet. Why should the feet only be set aside as the part of the body to which support should be applied as a preventive measure? The advisability of support for the feet depends upon the individual case just as the authors point out in discussing shoulder braces and abdominal supports in another paragraph.

The authors' conclusion "the environment factors in the posture of the well pre-school child are therefore confined chiefly to the feet" if accepted literally will produce in one's mind a conception of body mechanics which is not in accordance with physiologic facts. The feet are only part of the whole mechanics of the body concerned in bipedal stance and locomotion. An imbalance produced by deformity of the feet must be counterbalanced by a deformity or at least a deviation in the opposite direction in some other part of the body. Conversely a deformity or deviation in some other part of the body may have its opposite compensating or balancing deformity in the feet. Correction of the foot deformity if properly done will have a beneficial effect on the general body mechanics. However, if the foot condition is thought of too exclusively of its relationship to the rest of the body, harmful overcorrection may result.

CLIFFORD SWEET.

The Early History of The Infant Welfare Movement. G. F. McCleary, London, 1933, H. K. Lewis & Co., pp. 176.

An interesting and readable account of the origins of the Infant Welfare Movement. While dealing chiefly with the movement in England, the discussion of the French influence is adequately covered. The author stresses the importance of the early work of Dr. Nathan Strauss and Dr. Henry L. Coit in America and the emphasis placed upon milk. We recommend the reading of the book by the younger pediatricians who step into work in the fully developed welfare center of today.

BORDEN VEEDER.

Therapeutique Hydro-climatologique en Pédiatrie. P. Nobécourt and G. Boulanger-Pilet. Paris. Masson et Cie, 1933, pp. 195.

A discussion of the indications for hydrotherapy and climate in various conditions in infancy and childhood. A list of the principal thermal and climatic stations in France is given.

B. S. V.

The Clinical Study and Treatment of Sick Children. John Thomson and Leonard Findlay. Edinburg. Oliver and Boyd, 1933, pp. 1075.

A fifth edition of Dr. Thomson's well-known textbook by Dr. Findlay. The revision is excellent and in keeping with the high standard set by Dr. Thomson in the first edition some thirty-five years ago.

B. S. V.

Comments

FROM reports we have heard and a reading of the minutes of the recent Child Health Recovery Conference called by the "Children's Bureau," and held in Washington on October 6, the impression is obtained that the gun was fired at the stars to shoot the rabbit on the ground. It is quite obvious, to the interested observer, that some one became quite disturbed over the fact that many children in the present period of economic distress and revolution were not getting sufficient food to keep them in good health and from being hungery. Therefore, something should and must be done about it. With this no one can disagree. It is a question of necessary relief.

The proposition that was outlined and a group called to Washington to adopt was a nationwide examination of children for malnutrition; this to be carried out by the respective states under the general guidance of the Children's Bureau. This is quite a different matter. The basic error, of course, lies in thinking of malnutrition and insufficient food as one and the same thing. That insufficient food may lead to malnutrition if continued for a long period is, of course, a fact. Up to the present time, at least, insufficient food has been one of the more rare and uncommon causes of malnutrition. Where food has been a factor in malnutrition, it has been associated with faulty food habits, unbalanced diet, and the like, rather than with a lack of food. The common causes of malnutrition are found chiefly in disease, physical defects, fatigue, and faulty habit formation.

It should not be difficult through our regular social agencies who are handling relief, to find those children who actually are getting too little food. Give them the food. Do it rapidly and at once. But to red tape this around "malnutrition" and elaborate medical examination on blanks furnished by the Children's Bureau is shooting rather wildly into the air.

What, it may seriously be asked, does the government propose to do? If malnutrition is the goal, does the government intend to provide convalescent homes for the thousands of malnourished children with an underlying cardiac or tuberculous lesion, or bloody holidays when tonsils and adenoids are removed by the thousands? If "malnutrition" as shown by a medical examination is the basis for giving extra food to hungry children who need it, the only logical thing is for the government to provide relief for children malnourished from other causes. It is rather an absurd situation.

From a more practical standpoint as physicians we must ask first of all what standards are to be used. It has taken years and will continue to take years to overcome the misuse and misapplication of height-weight-age tables of measurement as applied to malnutrition. This, if we recall it correctly, was largely the result of the measuring and weighing campaign of the Children's Bureau. There is danger of "food and malnutrition" being linked together in the minds of the laity as one and the same thing, if a "malnutrition" campaign on the basis outlined is made a propaganda movement by the Children's Bureau.

We are strongly in favor of food relief for children who need it. We are further in favor of the careful medical study of malnourished children and the application

of indicated remedial measures. This latter is a time-taking process and a continuous need, and one which is under way in many of our cities and in some of our states. For example, the work in Pennsylvania was outlined by Dr. Hamill in his recent presidential address in the September number of the Journal. We feel, however, that the conference in Washington exhibited a lot of loose thinking and mixed up some simple direct things in a complicated unnecessary way.

This is an expression of personal reaction and opinion. Doubtless, many will disagree. This column, as has been stated several times, is an open forum for the discussion of pediatric subjects and is open to those who hold opinions which differ. Quite obviously with such a purpose in view, it cannot be regarded as the "official voice" of the Academy of Pediatrics. Academy discussions and actions are printed under the head of Academy Proceedings.

BEGINNING with the January number, the Journal will make a past to present change. The interesting series of eighteen articles on Pediatric Antiques by Dr. Drake of Toronto will end with the present number. In January the first of a series of articles on "American Pediatric Clinics" will appear. Twelve outstanding clinics have been selected by the Editorial Board. Although there has been some objection on the score of "modesty," the Journal has requested that the individual clinics be described by the Chief of Staff or someone who has been intimately connected with the clinic for a number of years rather than by an outside reporter. The scope of the articles will include the history and aims of the clinic, physical and clinical facilities, house officers, and research facilities. If the series is as interesting as the Editorial Board expects, it will be followed by one on foreign pediatric centers. The Editors wish to take this opportunity to express their thanks to Dr. Drake for the time and study he has given to the series of special articles closing with this number.

WE WELCOME the first number of the *Indian Journal of Pediatrics*, published in Calcutta. The Journal, which is to appear quarterly, is published in English and is edited by K. C. Chaudhuri. The first number contains a foreword by Sir Nilratan Sircar, a Birthday Greeting by Dr. Robert Hutchinson, and an Introduction by Czerny. The contents contain several original articles, society proceedings, book reviews and abstracts. May it live and prosper.

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

Official Organ for The American Academy of Pediatrics

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VOLUME III

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